ملحق

نبذة عن حياة الأستاذ الدكتور حسين محمد دشتي وسيرته الذاتية

النظام الغذائي

لعلاج الأمراض المتعلقة بالسمنة

البروفيسور حسين محمد دشتي
أستاذ دكتور في قسم الجراحة
كلية الطب
مركز العلوم الطبية
جامعة الكويت

بسم الله الرحمن الرحيم

قال الله تعالى:

﴿ وَلَقَدْ خَلَقْنَا الْإِنسَانَ مِن سُلَالَةٍ مِّن طِينٍ ثُمَّ جَعَلْنَاهُ نُطْفَةً فِي قَرَارٍ مَّكِينٍ ثُمَّ خَلَقْنَا النُّطْفَةَ عَلَقَةً فَخَلَقْنَا الْعَلَقَةَ مُضْغَةً فَخَلَقْنَا الْمُضْغَةَ عِظَامًا فَكَسَوْنَا الْعِظَامَ لَحْمًا ثُمَّ أَنشَأْنَاهُ خَلْقًا آخَرَ فَتَبَارَكَ اللَّهُ أَحْسَنُ الْخَالِقِينَ ﴾

صدق الله العظيم

سورة المؤمنون آية (١٢ - ١٣)

يا ظبية البان ترعى في خمائله ... ليهنكِ اليوم أن القلب مرعاك
الماء عندك مبذول لشاربه ... وليس يرويك إلا مدمعي الباكي
هبّت لنا من رياح الغور رائحة ... بعد الرقاد عرفناها برياك
ثم انثنينا إذا ما هزنا طرب ... على الرحال تعللنا بذكراك
سهم أصاب وراميه بذي سَلَمٍ ... من بالعراق لقد أبعدتِ مرماك
وعد لعينيك عندي ما وفيتِ به ... يا قرب ما كذبت عينيّ عيناك
حكت لحاظكِ ما في الريم من مُلحٍ ... يوم اللقاء فكان الفضل للحاكي
كأن طرفكِ يوم الجزع يخبرنا ... بما طوى عنكِ من أسماء قتلاكِ
أنتِ النعيم لقلبي والعذاب له ... فما أمرّك في قلبي وأحلاكِ
عندي رسائل شوقٍ لست أذكرها ... لولا الرقيب لقد بلّغتها فاكِ
سقى مني وليالي الخيف ما شربت ... من الغمام وحياها وحياكِ
إذ يلتقي كل ذي دَين ومأطله ... منا ويجتمع المشكوّ والشاكي
لما غدا السرب يعطو بين أرحلنا ... ما كان فيه غريم القلب إلاكِ
هامت بك العين لم تتبع سواكِ هوى ... من علّم البين أن القلب يهواكِ
حتى دنا السرب ما أحييتِ من كمدٍ ... قتلى هواكِ ولا فاديتِ أسراكِ
يا حبّذا نفحة مرت بفيك لنا ... ونطفة غُمست فيها ثاياكِ

الشريف الرضي
٩٦٩- ١٠١٥ م

فهرس
الجـزء الخامس

الصحة تاج على رؤوس الأصحاء

نبذة عن حياة أ.د / حسين محمد دشتي في صور

الأمير القائد
سمو الشيخ / صباح الأحمد الجابر الصباح

نبذة عن حياة أ.د / حسين محمد دشتي في صور

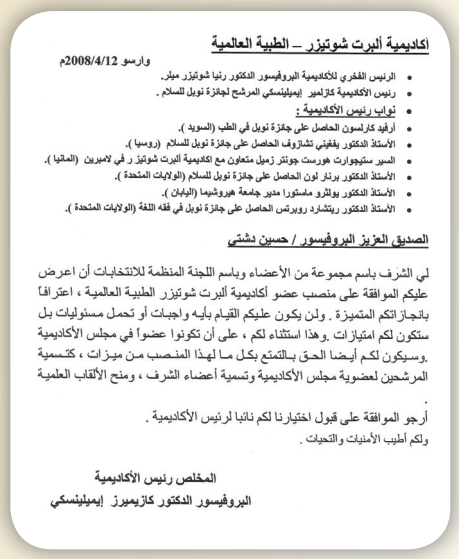
سمو أمير البلاد المغفور له بإذن الله الشيخ جابر الأحمد الجابر الصباح يشمل برعايته لقاء الدكتور حسين دشتي بعد حصوله على جائزة الأكاديمية البولندية العالمية في مجال الطب والإنسانية

نبذة عن حياة أ.د / حسين محمد دشتي في صور

سمو الأمير الراحل أثناء مقابلته الدكتور دشتي وزملائه عند حصوله على جائزة الانتاج العلمي لعام ١٩٩٤ م .

سمو ولي العهد يستقبل البروفسور الدكتور حسين دشتي بمناسبة حصوله على منصب نائب الاكاديمية العالمية (ألبرت شوايتزر)

نبذة عن حياة أ.د / حسين محمد دشتي في صور



اكاديمية ألبرت شوتيزر – الطبية العالمية

وارسو 2008/4/12م

- الرئيس الفخري للأكاديمية البروفيسور الدكتور رتبا شوتيزر مباد.
- رئيس الأكاديمية كازيمير إيميليتسكي المرشح لجائزة نوبل للسلام .

نواب رئيس الأكاديمية :

- أرفيد كارلسون الحاصل على جائزة نوبل في الطب (السويد).
- الأستاذ الدكتور يفغيني تشازوف الحاصل على جائزة نوبل للسلام (روسيا).
- السير ستيجوارت هورست جونتر زميل متعاون مع اكاديمية ألبرت شوتيزر في لامبرين (المانيا).
- الأستاذ الدكتور برنار لون الحاصل على جائزة نوبل للسلام (الولايات المتحدة).
- الأستاذ الدكتور يوتارو ماسنورا مدير جامعة هيروشيما (اليابان).
- الأستاذ الدكتور رينشارد روبرتس الحاصل على جائزة نوبل في فقه اللغة (الولايات المتحدة).

الصديق العزيز البروفيسور / حسين دشتي

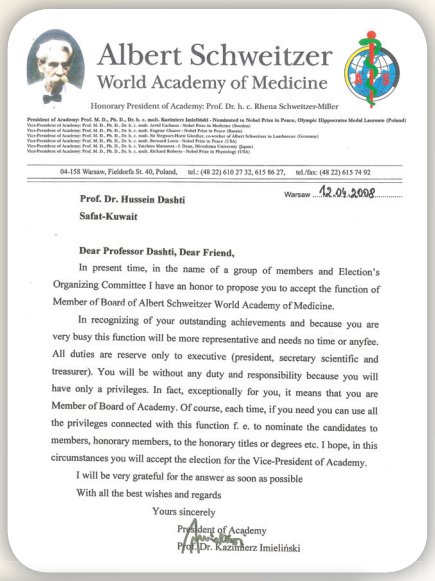
لي الشرف باسم مجموعة من الأعضاء وباسم اللجنة المنظمة للانتخابات أن اعرض عليكم الموافقة على منصب عضو أكاديمية ألبرت شوتيزر الطبية العالمية ، اعترافا بانجازاتكم المتميزة . ولن يكون عليكم القيام بأيه واجبات أو تحمل مسئوليات بل ستكون لكم امتيازات .وهذا استثناء لكم ، على أن تكونوا عضوا في مجلس الأكاديمية .وسيكون لكم أيضا الحق بالتمتع بكل ما لهذا المنصب من ميزات ، كتسمية المرشحين لعضوية مجلس الأكاديمية وتسمية أعضاء الشرف ، ومنح الألقاب العلمية .

أرجو الموافقة على قبول اختيارنا لكم نائبا لرئيس الأكاديمية .

ولكم أطيب الأمنيات والتحيات .

المخلص رئيس الأكاديمية

البروفيسور الدكتور كازيميرز إيميليتسكي



Albert Schweitzer
World Academy of Medicine

Honorary President of Academy: Prof. Dr. h. c. Rhena Schweitzer-Miller

04-158 Warsaw, Fieldorfa St. 40, Poland, tel.: (48 22) 610 27 32, 615 86 27, tel./fax: (48 22) 615 74 92

Warsaw 12.04.2008

Prof. Dr. Hussein Dashti
Safat-Kuwait

Dear Professor Dashti, Dear Friend,

In present time, in the name of a group of members and Election's Organizing Committee I have an honor to propose you to accept the function of Member of Board of Albert Schweitzer World Academy of Medicine.

In recognizing of your outstanding achievements and because you are very busy this function will be more representative and needs no time or anyfee. All duties are reserve only to executive (president, secretary scientific and treasurer). You will be without any duty and responsibility because you will have only a privileges. In fact, exceptionally for you, it means that you are Member of Board of Academy. Of course, each time, if you need you can use all the privileges connected with this function f. e. to nominate the candidates to members, honorary members, to the honorary titles or degrees etc. I hope, in this circumstances you will accept the election for the Vice-President of Academy.

I will be very grateful for the answer as soon as possible

With all the best wishes and regards

Yours sincerely

President of Academy
Prof. Dr. Kazimierz Imieliński

دشتي ينال منصب نائب رئيس أكاديمية ألبرت شوتيزر

كونا – حاز البروفيسور في قسم الجراحة بجامعة الكويت د. حسين دشتي على منصب نائب رئيس اكاديمية «البرت. شوتيزر» الطبية العالمية ومقرها وارسو.

وقال الدكتور دشتي، وهو ايضا استشاري البرنامج الغذائي الكيتوني لـ«كونا» امس، ان ترشيحه للمنصب يعد مفخرة وانجازا علميا مهما، وهو حصيلة جهود متواصلة وانجازات متميزة كما ذكرت الاكاديمية في كتاب الترشيح. واضاف ان المنصب سيرشحه حسبما اكده رئيس الإكاديمية والمرشح لجائزة نوبل للسلام البروفيسور كازيميرز ايميليتسكي لمنح الالقاب العلمية للاطباء وتسمية المرشحين لعضوية مجلس الاكاديمية واعضاء الشرف

● حسين دشتي

المختلفة، وذلك حسب ٥ ابحاث علمية

واستعرض النظام قائلا انه يركز على تناول اللحوم والدواجن والاسماك والبيض والخضروات الورقية لتخفيف الوزن الزائد، حيث يعمل الجسم بنظام الهدم والبناء.

واضاف ان الفريق الذي يرأسه، ويضم استاذ علم الفيزيولوجي بكلية الطب في جامعة الكويت الدكتور ناجي الزيد، ورئيس قسم الجراحة بكلية الطب الدكتور سامي اصفر والدكتور طالب حسين وغيرهم حصل على جائزة افضل بحث طبي بكلية الطب في جامعة الكويت قبل ٤ سنوات.

واشار الى ان البحث الفائز تناول تاثير البرنامج الكيتوني على الجسم، لا سيما تخفيض نسبة

القبس العدد رقم ١٢٥٧٠ بتاريخ ٢٥ / ٩/٥ ٢٠٠٨ صفحة رقم ٦

نبذة عن حياة أ.د / حسين محمد دشتي في صور

تحت رعاية وزير الإعلام

مجلة العصر

تقييم احتفالاً لتكريم

البروفيسور / حسين دشتي

الصورة تبين وزير الأشغال والبلدية الدكتور فاضل صفر

البروفيسور / حسين محمد دشتي

الفائز بجائزة مجلة العصر لأعمال المتميزة عام ٢٠٠٥ عن (الصحة والطب)

التخصصات: دكتوراه من جامعة لوند بالسويد- رئيس قسم التشريح بجامعة الكويت- أستاذ جراحة بجامعة الكويت- تخصص رفيع بالمعادن النادرة- مكتشف نظام الكيتوني لعلاج السمنة.

العضويات: عضو مؤسس في الجمعية الدولية عن المعادن النادرة في الجسم- عضو مؤسس في لجنة الأفروآسيوية لهيئة التقدم في البحوث عن المعادن النادرة. الخبرات: محرر في مجلة الطب الأمريكية للتغذية- محرر سابق في مجلة MMP جامعة الكويت – جراح في مستشفى الأميري.

الجوائز التي حاز عليها: حصل على الجائزة والميدالية الذهبية من جامعة كاستربا في مجال السرطان- جائزة أفضل بحث علمي من سويسرا -حصل على جائزة ألبرت شوايتزرت الطبية الذهبية رفيعة المستوى من الأكاديمية البولندية العالمية للعلوم الطبية- جائزة مجلة العصر للأعمال المتميزة.

المؤلفات: لديه العديد من الكتب والأبحاث الطبية. أشهرها كتاب (النظام الغذائي لعلاج الأمراض المتعلقة بالسمنة) الذي أعيدت طباعته عدة مرات خلال سنتين وبيع منه عشرات الآلاف من النسخ في منطقة الخليج.

مجلة العصر ذو القعدة ١٤٢٦ هـ - ديسمبر ٢٠٠٥

د/ دشتي مع د/ صادق السلمان والتشكيلي قاسم ياسين والمستشار الإعلامي / محسن دشتي

نبذة عن حياة أ.د / حسين محمد دشتي في صور

د/ دشتي أثناء استلامه جائزة من البروفيسور علي الشملان

أطباء كويتيين يخضعون ٦٣ مريضا كويتيا مصابين بالسمنة لاختبار علمي

د. حسين دشتي:

كلوا الدهون تقضوا على السمنة!

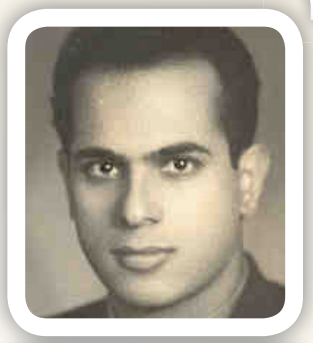
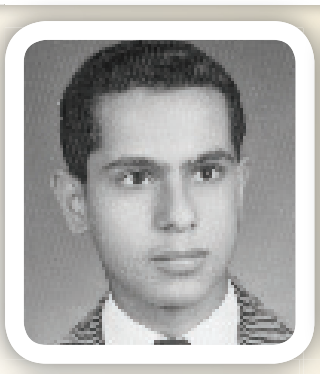
د. حسين دشتي

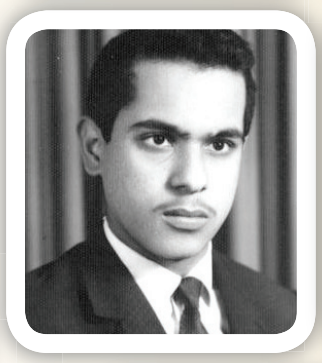
ALSEYASSAH Saturday 6th Juli 2002 - (35th Year) Issue No 12073

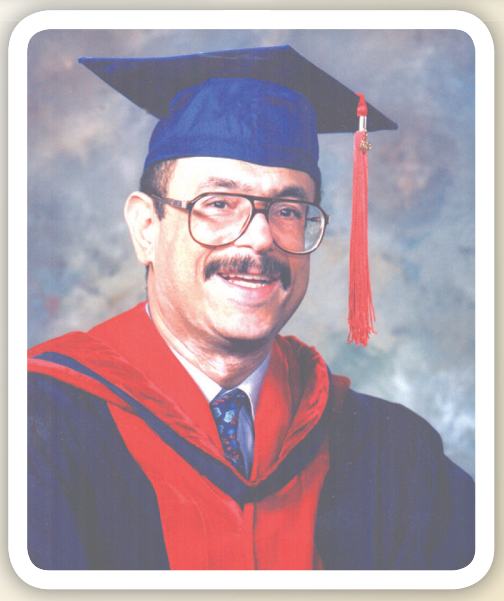
من دون أدوية وبلا عمليات جراحية

علاج مرض السمنة بنظام غذائي صحي في كلية الطب في جامعة الكويت

نبذة حياة أ.د / حسين محمد دشتي في صور

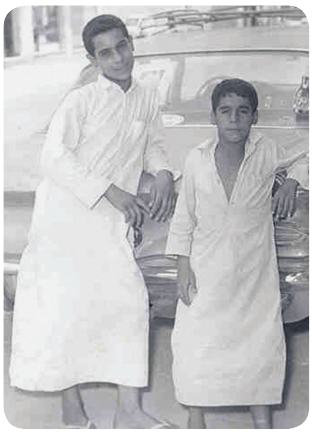




نبذة حياة أ.د / حسين محمد دشتي في صور

مع العائلة عام ١٩٧٢



أثناء طفولتي في منطقة الشرق

مع الدكتور صادق السلمان والعميد الركن باقر السلمان

مع المرحوم السيد عبد الله الدخيل في المدرسة المباركية

في منطقة الشرق عام ٥٦

نبذة عن حياة أ.د / حسين محمد دشتي في صور

د/ دشتي بالمدرسة المباركية لعام ٦٣

د/ دشتي أثناء الدراسة
بالمدرسة الجعفرية الوطنية

د/ دشتي أثناء الطفولة بمنطقة الشرق

د/ دشتي أثناء الأحتفال بالعيد

د/ دشتي مع مجموعة من الزملاء
بالصف الثالث الثانوي

د/ دشتي مع المرحوم عبد الله ادخيل

نبذة حياة أ.د / حسين محمد دشتي في صور

د/ دشتي مع د/ عبد الكريم سليم

د/ دشتي بسوق الخضرة

د/ دشتي بالصف الثاني الثانوي

د/ دشتي مع مجموعة من طلاب الطب بالهند

د/ دشتي بمدرسة المباركية المتوسطة

د/ دشتي مع د/ عبد الكريم سليم
عضو المجلس البلدي

نبذة عن حياة أ.د / حسين محمد دشتي في صور

د/ دشتي مع مجموعة من الزملاء
بثانوية الشيخ لعام ٦٨

د/ دشتي مع ابناء أخوانه

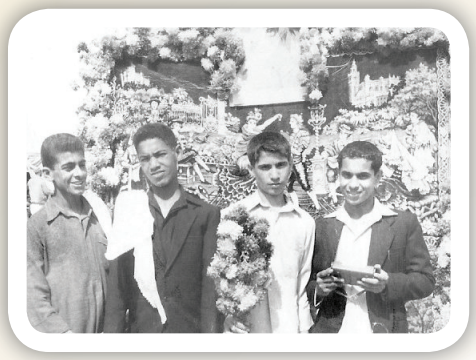
د/ دشتي مع مجموعة من الزملاء
بمنطقة الشرق

د/ دشتي بثانوية الشويخ
لعام ٦٤

في منطقة الشرق عام ٥٧

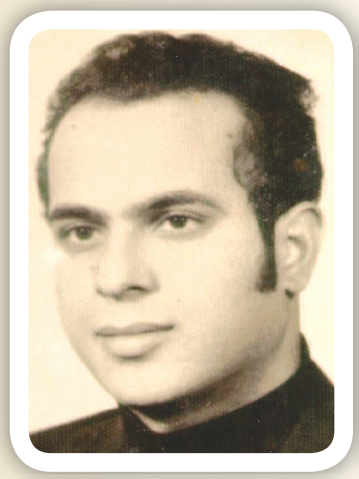
أثناء الدراسة في الهند عام ١٩٦٨

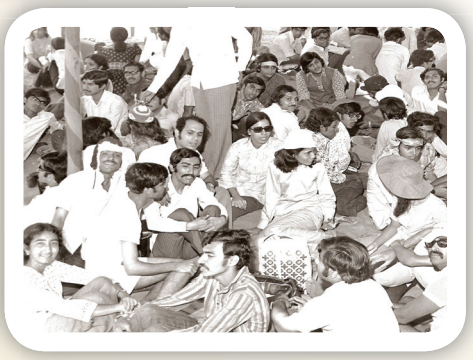
نبذة عن حياة أ.د / حسين محمد دشتي في صور



د/ دشتي يحتفل بالعيد سنة ١٩٥٨م

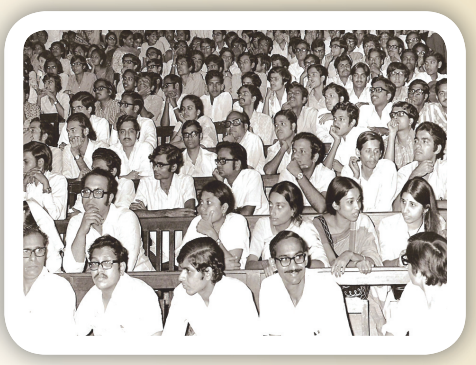
د/ دشتي في كلية الطب في الهند





أثناء الدراسة في مومباي سنة ١٩٦٨

نبذة عن حياة أ.د / حسين محمد دشتي في صور



على مقاعد الدراسة في كلية الطب بومباي

مع الفنان عزيز نازان

مع الممثل سانجاي دوث سنة ١٩٦٨ - بومباي
والزميل د/ طالب

مع الممثلة نرجس ١٩٦٨ بومباي

مع السيد / إبراهيم دشتي ١٩٧٢ بومباي

مع الشيخ جابر عبد الله الجابر ١٩٧٠بومباي

نبذة عن حياة أ.د / حسين محمد دشتي في صور

تقديم شهادة الدكتوراة للمرحوم
حمزة السلمان والمرحومة السلمان

د/ دشتي أثناء الدراسة بالهند

د/ دشتي مع رئيس مجلس الأمة السابق
السيد خالد الغنيم

د/ دشتي مع الزميل المرحوم الدكتور
جعفر أسيري

د/ دشتي مع أعضاء مجلس الأمة بمومباي

د/ دشتي أثناء الدراسة في كلية الطب في بومباي
سنة ١٩٦٠

نبذة عن حياة أ.د / حسين محمد دشتي في صور

الشيخ جابر عبد الله الجابر
والسيدعيسى يوسف القناعي ١٩٧٠

مع السيد / راشد الراشد في بومباي

مع بنجمارك ٨٦ عند الحصول على الدكتورة في السويد

مع الشيخ عيسى بن يوسف القناعي
بومباي ١٩٦٨

المدرسة العربية في بومباي ١٩٦٩

مع الشيخ جابر عبد الله الجابر ١٩٧٠بومباي

نبذة عن حياة أ.د / حسين محمد دشتي في صور

مراسم حصولي على الدكتوراة في السويد عام ١٩٦٨

د/ دشتي أثناء تسجيل اسمه في جامعة لوند بعد حصوله على الدكتوراه

د/ دشتي أثناء الأحتفال بحصوله على الدكتوره

د/ دشتي أثناء الاحتفال بحصوله على شهادة الدكتوراه بالسويد

د/ دشتي مع رئيس قسم الجراحة بكلية الطب بالسويد

نبذة عن حياة أ.د / حسين محمد دشتي في صور

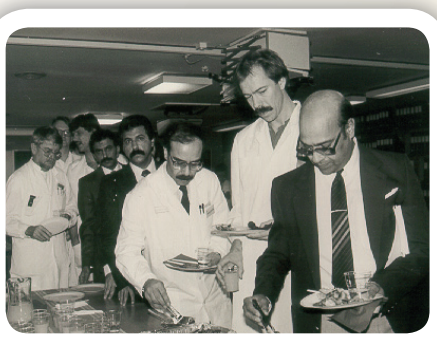
د/ دشتي مع السيد حسين الحريتي
نائب مجلس الأمة

د/ دشتي مع معالي وزير العدل والشؤون
القانونية ونائب رئيس مجلس الوزراء
السيد راشد الحماد

د/ دشتي مع عميد كلية الطب أثناء
حصوله على الدكتوراه

د/ دشتي أثناء تتويجه
بشهادة الدكتوراه بالسويد

د/ دشتي مع البروفيسور / بجنت
أثناء حصوله على الدكتوراه



د/ دشتي مع مجموعة من الزملاء بالسويد

نبذة عن حياة أ.د / حسين محمد دشتي في صور

د/ دشتي مع معالي وزير الصحة الدكتور
هلال الساير والدكتور محمد دشتي

د/ دشتي مع البروفيسور ناجي الزيد

البروفيسور ناجي الزيد
قسم القسيولوجي - جامعة الكويت

د/ دشتي مع البروفيسور عبد الطيف البدر
والبروفيسور عبدالله بهباني والأخ جاسم الخرافي

د/ دشتي بعد حصوله على شهادة الدكتوراه

د/ دشتي أثناء مناقشة رسالة الدكتوراه

نبذة عن حياة أ.د / حسين محمد دشتي في صور

كلية الطب - جامعة الكويت

أثناء إحتفال تخرج الأطباء

مع الدكتور هلال الساير
والبروفيسور سامي أصفر
كلية الطب

مع السفير البولندي ١٩٩٩ عند حصولي على جائزة ألبرت

نبذة عن حياة أ.د / حسين محمد دشتي في صور

مع نجم الهند دليب كمار عام ١٩٩٨

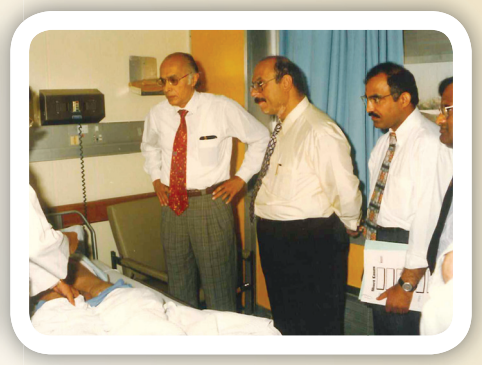
مع النجم عبد الحسين عبد الرضا

مع الزميل طالب منصور

مع المرحوم حيدر السلمان وبعض الأصدقاء

أثناء الاحتفال بحصولي على جائزة ألبرت شوتيزر عام ١٩٩٩

نبذة عن حياة أ.د / حسين محمد دشتي في صور



د/ دشتي مع البروفيسور موسى
من جامعة سانيجو

د/ دشتي مع لجنة المتحنين كلية الطب

د/ دشتي أثناء أمتحان السنة النهائية قسم الجراحة
كلية الطب ويبدو معالي وزير الصحة

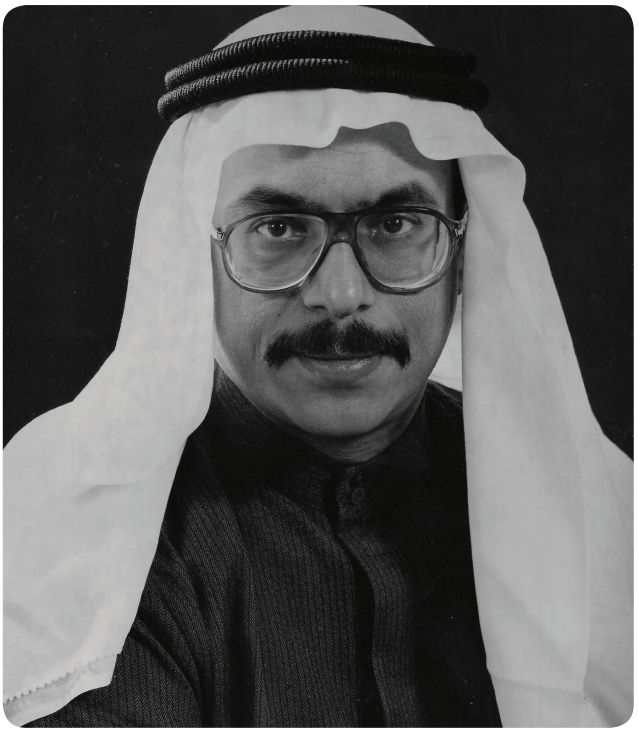
د/ دشتي لجنة الإمتحانات كلية الطب

د/ دشتي مع الممثل الهندي دليب كمار

نبذة عن حياة أ.د / حسين محمد دشتي في صور

مع العائلة

نبذة عن حياة أ.د / حسين محمد دشتي في صور



د/ دشتي مع ابنه وابن أخيه

نبذة عن حياة أ.د / حسين محمد دشتي في صور

الدكتور عبد اللطيف البدر والدكتور محمد دشتي

مع السيد / نيلسون مانديلا في كلية الطب

أثناء تخرج ابنائي من كلية الطب

مع إخواني حسن وعبد الرحمن دشتي

أثناء القاء محاضرة في السعودية ٢٠٠٨

مع د/ عبد اللطيف البدر ود/ هلال الساير وزير الصحة أثناء إحتفال التخرج

نبذة عن حياة أ.د / حسين محمد دشتي في صور

د/ دشتي مع بعض الوزراء الحاليين والسابقيين
لكلية طب الكويت

د/ دشتي مع الفنان داوود حسين
والدكتور صادق السلمان وابنه صادق دشتي

د/ دشتي مع الدكتورة فوزية الدريع

د/ دشتي مع الفنان حسين عبد الرضا
وبعض الممثلين والزملاء

د/ دشتي مع الممثلين الهنود

د/ دشتي مع قسم التشريح كلية الطب

نبذة عن حياة أ.د / حسين محمد دشتي في صور

مع أفراد العائلة والمخرجان جواد الأسدي والمرحوم كورمي وعلاء الجابر

مع أفراد العائلة والفنان رفيق على وعرفان رشيد ومجموعة من الصحفيين

د/ دشتي مع مخرج ومقدمة برنامج جمالك سودابة علي

مع الفنان رفيق على

مع نخبة من الممثلين للإحتفال بالفنان على سلطان سنة ٢٠٠٨

نبذة عن حياة أ.د / حسين محمد دشتي في صور

مع هيئة التدريس في كلية الطب

مع الزميل الدكتور حبيب أبل

مع الدكتور عبد الله بهبهاني

مع الدكتور عبد اللطيف البدر واملينكي وأبنائي
عام ١٩٩٨

مع الاساتذة الممتحنين في كلية الطب

نبذة عن حياة أ.د / حسين محمد دشتي في صور

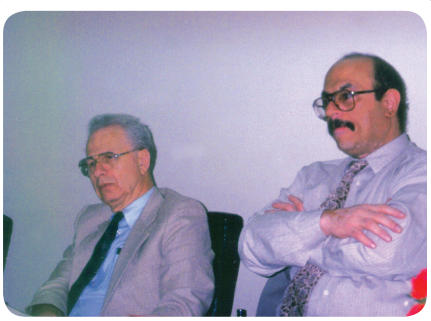
مع رئيس مجلس الأمة عند حصولي على جائزة ألبرت شواتيزر

مع د. حسن جوهر ، د. مهدي الموسوي وأبنائي

مع د. مصطفى الموسوي وأبنائى الأطباء المتخرجين

مع د. عبد اللطيف البدر ، د. عبد الله بهبهاني

مع د. هلال الساير، البروفيسور د. جوني



مع الجراح العالمي شوارتز أثناء إمتحان طلبة الطب

نبذة عن حياة أ.د / حسين محمد دشتي في صور

حصولي على جائزة أحسن بحث علمي في الغذاء الكيتوني

مع المرحوم الدكتور نائل النقيب

درع أفضل بحث علمي من البروفيسور مراد الحاصل على جائزة نوبل للطب

مع زملائي وإخواني

مع السفير الكندي ود. عبد اللطيف البدر ود. هلال الساير ود. مهدي الموسوي

مع الزميل محمود عبد العزيز أثناء الدراسة في الهند عام ١٩٧٠م

نبذة عن حياة أ.د / حسين محمد دشتي في صور

مع الشيخ أحمد الفهد والدكتور فؤاد عميد كلية الطب

مع الشيخ أحمد الفهد

مع الدكتور أناندبراساد

أثناء الاحتفال بحصولي على جائزة ألبرت شواتيزر سنة ١٩٩٨ م

مع رئيس مجلس الأمة وعميد كلية الطب ورئيس الاكاديمية والدكتور السلمان والزملاء

مع البروفيسور فيصل الناصر نائب مدير جامعة الخليج

نبذة عن حياة أ.د / حسين محمد دشتي في صور

د/ دشتي مع البروفيسير / اتاندابراساد

د/ دشتي مع الرئيس التنفيذي
لمؤسسة إتكنز

د/ دشتي مع مجموعة من زملائه
والدكتور هلال الساير وزير الصحة

د/ دشتي مع رئيس الأكاديمية العالمية للطب في بولندا

د/ دشتي مع مجموعة أساتذة الجراحة
في كلية الطب

نبذة عن حياة أ.د / حسين محمد دشتي في صور

د/ دشتي مع عبد الرحمن النجار
والدكتور عبد اللطيف البدر والدكتور حسين محمود
والدكتور فهد النجار

د/ دشتي مع الممتحنين بكلية الطب قسم الجراحة

د/ دشتي أثناء امتحان السنة النهائية بكلية الطب

د/ دشتي مع الدكتور عايد المناع والأستاذ جعفر محمد
قناة العدالة - برنامج اللوبي

د/ دشتي مع سفير الهند السابق والبروفيسير جان

د/ دشتي مع مجموعة من الزملاء
والدكتور عبد اللطيف البدر

نبذة عن حياة أ.د / حسين محمد دشتي في صور

المدرسة الوطنية الجعفرية ـ كويت

نتيجة اعمال التلميذ في السنة الدراسية ١٣٧٩ هـ. ـ ١٩٦٠ م.

اسم التلميذ : حسين محمد دشتي عمر التلميذ : ١٢ سنة متوسط عمر الفصل ١٢

السنة : الأولى المتوسطة . الفصل : ١ رقم الشهادة : ٢٣

المواد	الفروع	النهائيات: الكبرى	النهائيات: الصغرى	الدرجات: نصف السنة	الدرجات: آخر السنة	المجموع	الدرجة النهائية	الملاحظات
الشرعيات	القرآن الكريم	٥٠	٢٥	٣٢	٣١	٦٣	٣٢	
	الدين	٥٠	٢٥	٢٦	٢٧	٥٣	٢٧	
اللغات	اللغة العربية	١٠٠	٥٠	٦٨	٦٥	١٣٣	٦٧	
	اللغة الفارسية	١٠٠	٥٠	٧٢	٧٢	١٤٤	٧٢	
	اللغة الأنجليزية	١٠٠	٥٠	٦٢	٦٣	١٢٥	٦٣	
الرياضيات	الحساب	٨٠	٤٠	٢١	٢٠	٤١	٢١	
	الهندسة	٢٠	١٠	٠٧	١٠	١٧	١٤	
الاجتماعيات	التاريخ	٥٠	٢٥	٣٤	٣٧	٧١	٣٦	
	الجغرافيا	٥٠	٢٥	٣٦	٣٧	٧٣	٣٧	
مبادىء العلوم	الصحة	٥٠	٢٥	٢٧	٤٢	٦٩	٣٥	
	الاشياء	٥٠	٢٥	٢٨	٢٧	٥٥	٢٨	
الفنون	الرسم	٤٠	٢٠	٢٦	٢٥	٥١	٢٦	
	الاناشيد	٣٠	١٥	٢٠	٢١	٤١	٢١	
	التربية البدنية	٣٠	١٥	٢٠	٢٢	٤٢	٢١	
	المجموع الكلي	٨٠٠	٤٠٠	٤٨٩	٤٩٩	٩٨٨	٥٠٠	نتيجة التلميذ
	ترتيب التلميذ	الثالث والعشرون						[illegible]
	عدد تلاميذ الفصل	٢٧						ضاعف نشاطك
	السلوك والمواظبة	جيد جداً						واستعد للجولة القادمة
	عدد ايام الغياب					٢		أتمنى لك الفوز

اسم مربي الفصل: محمد حب الله — توقيعه — تاريخ صدور الشهادة: ٢٦/٦/١٩٦٠م — توقيع ناظر المدرسة (S. MUHD H. MUSAVI Kuwait)

المدرسة الوطنية الجعفرية ـ كويت

نتيجة عمل التلميذ لنصف السنة الدراسية لعام ١٣٨٠هـ ٦٠-٦١م

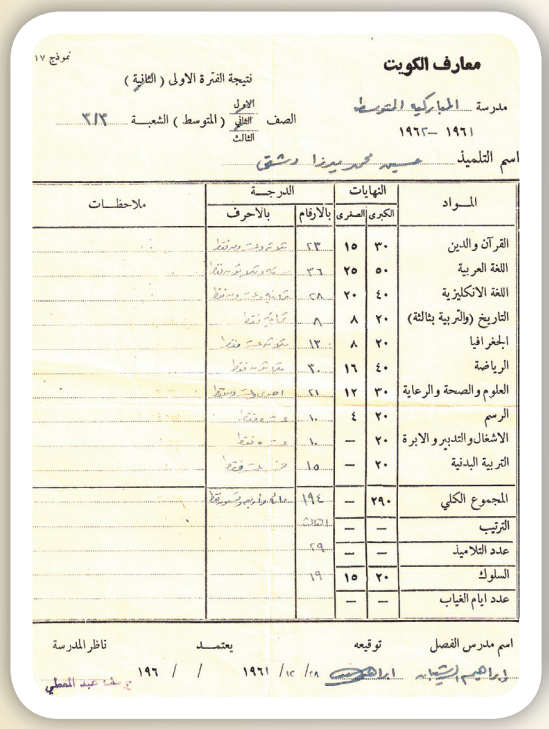
اسم التلميذ حسين محمد ميرزا عمر التلميذ ١٢ سنة و٤ أشهر متوسط عمر الفصل ١٣ سنة

السنة الثانية المتوسطة الفصل رقم الشهادة ٧

المواد	الفروع	النهايات: الكبرى	النهايات: الصغرى	الدرجة: بالارقام	الدرجة: بالاحرف	الملاحظات
الشرعيات	القرآن الكريم	٥٠	٢٥	٣٩	تسع وثلاثون	
	الدين	٥٠	٢٥	٣٢	اثنان وثلاثون	
اللغات	اللغة العربية	١٠٠	٥٠	٧١	احدى وسبعون	
	اللغة الفارسية	١٠٠	٥٠	٦٤	اربع وستون	
	اللغة الانجليزية	١٠٠	٥٠	٦٤	اربع وستون	
الرياضيات	الحساب	٨٠	٤٠	٤٥	خمس واربعون	
	الهندسة	٢٠	١٠	١٣	ثلاث عشرة	
الاجتماعيات	التاريخ	٥٠	٢٥	٤٥	خمس واربعون	
	الجغرافيا	٥٠	٢٥	٢٥	خمس وعشرون	
مبادى العلوم	الصحة	٥٠	٢٥	٣٤	اربع وثلاثون	
	الاشياء	٥٠	٢٥	٤٠	اربعون	
الفنون	الرسم	٤٠	٢٠	٢٦	ست وعشرون	
	الاناشيد	٣٠	١٥	٢٥	خمس وعشرون	
	التربية البدنية	٣٠	١٥	٢٢	اثنان وعشرون	
	المجموع الكلي	٨٠٠	٤٠٠	٥٤٥	خمسمائة وخمس واربعون	
	الترتيب			١١	الحادي عشر	نهنئك على تحاصل
	عدد تلاميذ الفصل			١٩	تسع عشرة	ارجو لك دوام
	السلوك والمواظبة	٢٠	١٠	٢٠	عشرون	التقدم والاطراد النجاح
	عدد ايام الغياب				لم يتغيب	

اسم مربي الفصل: سيد محمود شاه — توقيعه — تاريخ صدور الشهادة: ٢٧/٨/١٣٨٠هـ — توقيع ناظر المدرسة (S. MUHD H. MUSAVI Kuwait)

نبذة عن حياة أ.د / حسين محمد دشتي في صور



نموذج ١٧

معارف الكويت

نتيجة الفترة الاولى (الثانية)

مدرسة المباركية المتوسطة — السنة ١٩٦١ – ١٩٦٢

الصف الاول الثاني الثالث (المتوسط) الشعبة ٢/١

اسم التلميذ حسين محمد حيدر دشتي

المواد	النهايات الكبرى	النهايات الصغرى	الدرجة بالارقام	الدرجة بالاحرف	ملاحظات
القرآن والدين	٣٠	١٥	٢٣		
اللغة العربية	٥٠	٢٥	٣٦		
اللغة الانكليزية	٤٠	٢٠	٢٨		
التاريخ (والتربية بثالثة)	٢٠	٨	٨		
الجغرافيا	٢٠	٨	١٢		
الرياضة	٤٠	١٦	٢٠		
العلوم والصحة والرعاية	٣٠	١٢	٢١		
الرسم	٢٠	٤	١٠		
الاشغال والتدبير والابرة	٢٠	—	١٠		
التربية البدنية	٢٠	—	١٥		
المجموع الكلي	٢٩٠	—	١٩٤		
الترتيب	—	—	الثالث		
عدد التلاميذ	—	—	٢٩		
السلوك	٢٠	١٥	١٩		
عدد ايام الغياب	—	—	—		

اسم مدرس الفصل ابراهيم [illegible] توقيعه [illegible] يعتمد ١٩٦١/١٢/٢٨ ناظر المدرسة يوسف عبد المطلبي

نموذج ١٨

معارف الكويت

مدرسة المباركية — السنة ١٩٦٤ – ١٩٦٥

نتيجة الفترة الاولى (الثانية)

السنة الرابعة (متوسط) الفصل ثالث

اسم التلميذ حسين محمد حيدر دشتي

المواد	النهايات الكبرى	النهايات الصغرى	الدرجة بالارقام	الدرجة بالاحرف	ملاحظات
القرآن والدين	٣٠	١٥	٢٧	سبع وعشرون	
اللغة العربية	٥٠	٢٥	٤٠	أربعون	
اللغة الانكليزية	٤٠	١٦	٢٩	تسع وعشرون	
التاريخ والتربية الوطنية	٣٠	١٢	٢٢	اثنان وعشرون	
الجغرافيا	٢٠	٨	١٤	اثنا عشر	
الرياضة	٤٠	١٦	٢٣	ثلاث وعشرون	
العلوم والصحة والرعاية	٣٠	١٢	٢٣	ثلاث وعشرون	
الرسم	٢٠	٤	١٣	ثلاث عشرة	
المجموع الكلي	٢٦٠	١٣٠	١٨٩	مائة وتسع وثمانون	
الترتيب	—	—	١	الأول	
عدد التلاميذ	—	—	٢٩	تسع وعشرون	
الاشغال والتدبير والابرة	٢٠	—	١٣	ثلاث عشرة	
التربية البدنية	٢٠	—	١٣	ثلاث عشرة	
السلوك	٢٠	١٥	٢٠	عشرون	
عدد ايام الغياب	—	—	٧	سبعة ايام	

اسم مدرس الفصل [illegible] توقيعه [illegible] يعتمد ١٩٦٤/١٢/٢٠ ناظر المدرسة [illegible]

نبذة عن حياة أ.د / حسين محمد دشتي في صور

المواد	النهاية العظمى	النهاية الصغرى	الفترة الأولى	الفترة الثانية	مجموع الفترتين	درجة اعمال السنة ⅛ مجموع الفترتين اي ¼ النهاية الكبرى	درجة الامتحان التحريري النقل ¾ النهاية الكبرى	الدرجة النهائية
الدين	٢٠	١٠	١٧	١٩	٣٦	أربعة ونصف ٤½	١٢¾	١٧
اللغة العربية	٤٠	٢٠	٣٣	٣٤	٦٧	ثمانية ونصف ٨½	٢٢	٣٠½
اللغة الاجنبية	٤٠	١٦	٣٠	٢٨	٥٨	سبعة ونصف ٧½	١٧	٢٤½
التاريخ والمجتمع	٣٠	١٢	٢٦	٢٥	٥١	ستة ونصف ٦½	١٦¾	٢٣
الجغرافيا	٣٠	١٢	٢٣	٢٥	٤٨	ستة ٦	١٩	٢٥
الرياضة	٤٠	١٦	٣٥	٣٩	٧٤	تسعة ونصف ٩½	١٨	٢٧½
العلوم العامة	٣٠	١٢	٢٢½	٢٨	٥٠½	ستة ونصف ٦½	١٨	٢٤½
الرسم	٢٠	٤	١٦	١٣	٢٩	ثلاث ونصف ٣½	١١	١٤½
مجموع درجات المواد	٢٥٠	١٢٥	٢٠٢½	٢١١				١٨٦½
الترتيب			[illegible]	[illegible]				٢٥م
عدد التلاميذ			٣٥	٣٥				٢٥٧

المواد الاضافية	الفترة الاولى	الفترة الثانية	درجة السنة	التقدير
الاشغال العملية				
الهوايات				
التربية البدنية و الالعاب				
عدد ايام الغياب بعذر مقبول	—	—		
عدد ايام الغياب بغير عذر مقبول	—	—		
درجة السلوك كبرى ٢٠ صغرى ١٥	٢٠/٢٠	٢٠/٢٠	/٢٠	

نتيجة التلميذ آخر العام

(١) ناجح و ينقل الى	(٢) راسب و يبقى للاعادة	٣ له دور ثان في
[illegible]		١ ..... ٢ ..... تاريخ الدور الثاني / / ١٩٦

توقيعات	الفترة الاولى	الفترة الثانية	آخر العام
مرشد الصف	[illegible]	[illegible]	
ناظر المدرسة	[illegible]	[illegible]	[illegible]
ولي أمر التلميذ	[illegible]	[illegible]	

وزارة التربية والتعليم
مدرسة [illegible] الثانوية
١٩٦٤/١٩٦٥

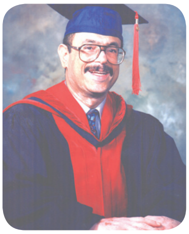
نتيجة اختبار نصف السنة
الصف الثانى الشعبة [illegible]

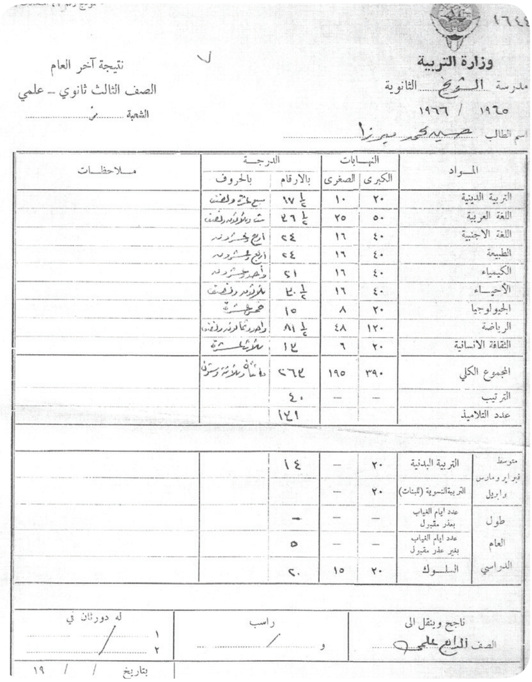
اسم الطالب [illegible]

المـــواد	النهايات الكبرى	النهايات الصغرى	درجة اختبار نصف السنة بالارقام	درجة اختبار نصف السنة بالحروف	ملاحظـات
القرآن الكريم والدين	٢٠	١٠	١٥½	خمسة عشر ونصف	
اللغة العربية	٤٠	٢٠	٢٤	أربع وعشرون درجة	
اللغة الانجليزية	٤٠	١٦	٢٤	أربع وعشرون درجة	
التاريخ والمجتمع	٣٠	١٢	٢٢	اثنان وعشرون درجة	
الجغرافيا	٣٠	١٢	٢٢	اثنان وعشرون درجة	
الرياضـة	٤٠	١٦	٢٩½	تسع وعشرون ونصف	
الطبيعـة	٣٠	١٢	٢٨	ثمان وعشرون درجة	
الكيميـاء	٣٠	١٢	٢٥	خمس وعشرون درجة	
الأحيـاء	٢٠	٨	١٥	خمس عشرة فقط	
الجيولوجيا	٢٠	٨	١٩	تسع عشرة فقط	
التربيـة الفنية	٢٠	٤	١٤	أربع عشرة فقط	
المجمـوع	٣٢٠	١٦٠	٢٤٨	مائتان وثمانية وأربعون	
التربية النسوية « للبنات »	٢٠	—			
التربية البدنية	٢٠	—			
المجموع الكلي للبنين	٣٤٠	—			
المجموع الكلي للبنات	٣٦٠	—			
الترتيب	—	—	الرابع		
عدد التـلاميذ	—	—	٤١		
عدد أيام الغياب بعذر مقبول	—	—			
عدد أيام الغياب بغير عذر مقبول	—	٢			
السـلوك	٢٠	١٥			

كتبـه راجعـه

نبذة عن حياة أ.د / حسين محمد دشتي في صور





١٦٤٤

وزارة التربية

مدرسة الشويخ الثانوية

١٩٦٥ / ١٩٦٦

اسم الطالب حسين محمد ميرزا

نتيجة آخر العام

الصف الثالث ثانوي ـ علمي

الشعبة م

المـواد	النهايات الكبرى	النهايات الصغرى	الدرجة بالارقام	الدرجة بالحروف	مـلاحظـات
التربية الدينية	٢٠	١٠	١٧ ½	[illegible]	
اللغة العربية	٥٠	٢٥	٢٦ ½	[illegible]	
اللغة الاجنبية	٤٠	١٦	٢٤	أربع وعشرون درجة	
الطبيعة	٤٠	١٦	٢٤	أربع وعشرون درجة	
الكيمياء	٤٠	١٦	٢١	واحد وعشرون درجة	
الأحيـاء	٤٠	١٦	٢٠ ½	[illegible]	
الجيولوجيا	٢٠	٨	١٥	خمس عشرة	
الرياضة	١٢٠	٤٨	٨١ ½	[illegible]	
الثقافة الانسانية	٢٠	٦	١٢	[illegible]	
المجموع الكلي	٣٩٠	١٩٥	٢٦٤	[illegible]	
الترتيب	—	—	٤٠		
عدد التلاميذ			١٤١		

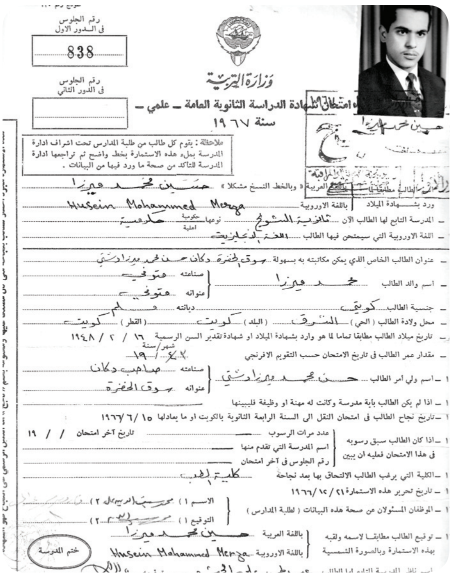
		الكبرى	الصغرى	الدرجة	
متوسط فبراير ومارس وابريل	التربية البدنية	٢٠	—	١٤	
	التربية النسوية (للبنات)	٢٠	—		
طول العام الدراسي	عدد ايام الغياب بعذر مقبول	—	—	—	
	عدد ايام الغياب بغير عذر مقبول	—	—	٥	
	السلـوك	٢٠	١٥	٢٠	

ناجح وينقل الى الصف الرابع علمي

راسب و ...

له دورثان في ١ ... ٢ ...

بتاريخ / / ١٩



رقم الجلوس في الدور الاول 838

رقم الجلوس في الدور الثاني

وزارة التربية

امتحان شهادة الدراسة الثانوية العامة ـ علمي ـ

سنة ١٩٦٧

ملاحظة : يقوم كل طالب من طلبة المدارس تحت اشراف ادارة المدرسة بملء هذه الاستمارة بخط واضح ثم تراجعها ادارة المدرسة للتأكد من صحة ما ورد فيها من البيانات .

اسم الطالب مطابقا لما ورد بشهادة الميلاد باللغة العربية « وبالخط النسخ مشكلا » حسين محمد ميرزا

باللغة الاوروبية Husein Mohammed Merza

ـ المدرسة التابع لها الطالب الآن ثانوية الشويخ نوعها حكومية / اهلية حكومية

ـ اللغة الاوروبية التي سيمتحن فيها الطالب اللغة الانجليزية

ـ عنوان الطالب الخاص الذي يمكن مكاتبته به بسهولة سوق الحضرة دكان حسن محمد ميرزا دشتي

ـ اسم والد الطالب محمد ميرزا صناعته متوفى عنوانه متوفى

ـ جنسية الطالب كويتي ديانته مسلم

ـ محل ولادة الطالب (الحي) المشرق (البلد) كويت (القطر) كويت

ـ تاريخ ميلاد الطالب مطابقا تماما لما هو وارد بشهادة الميلاد او شهادة تقدير السن الرسمية ١٦ / ٢ / ١٩٤٨

ـ مقدار عمر الطالب في تاريخ الامتحان حسب التقويم الافرنجي شهر/سنة ١٩ / ١٠

١ ـ اسم ولي امر الطالب حسن محمد ميرزا دشتي صناعته صاحب دكان عنوانه سوق الحضرة

١ ـ اذا لم يكن الطالب بأية مدرسة وكانت له مهنة او وظيفة فليبينها

١ ـ تاريخ نجاح الطالب في امتحان النقل الى السنة الرابعة الثانوية بالكويت او ما يعادلها ١٥ / ٦ / ١٩٦٦

١ ـ اذا كان الطالب سبق رسوبه في هذا الامتحان فعليه ان يبين: عدد مرات الرسوب ــ تاريخ آخر امتحان / / ١٩ ؛ اسم المدرسة التي تقدم منها ــ ؛ رقم الجلوس في آخر امتحان ــ

١ ـ الكلية التي يرغب الطالب الالتحاق بها بعد نجاحه كلية الطب

١ ـ تاريخ تحرير هذه الاستمارة ٢١ / ١٢ / ١٩٦٦

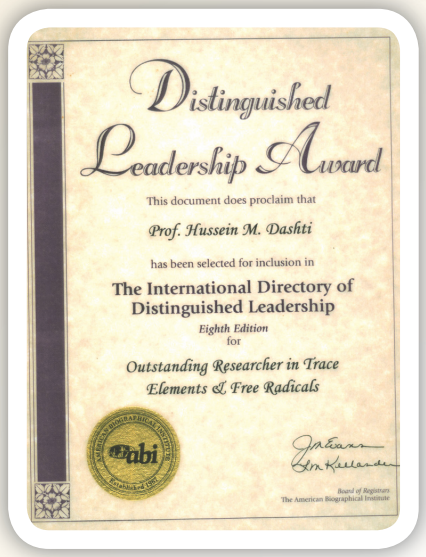
١ ـ الموظفان المسئولان عن صحة هذه البيانات (لطلبة المدارس) الاسم ١) [illegible] ٢) التوقيع ١) [illegible] ٢)

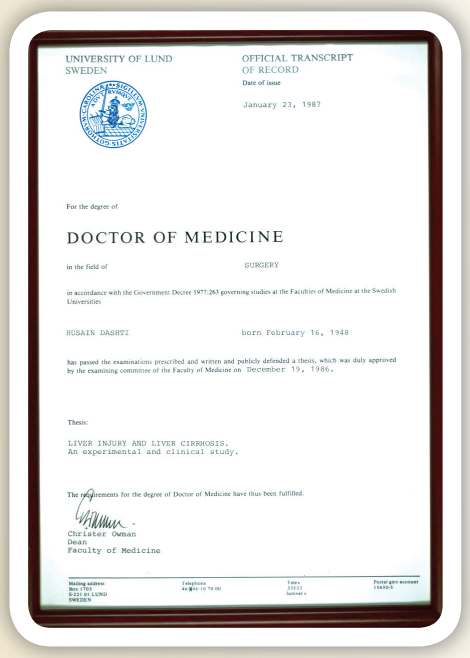
١ ـ توقيع الطالب مطابقا لاسمه ولقبه بهذه الاستمارة وبالصورة الشمسية باللغة العربية حسين محمد ميرزا باللغة الاوروبية Husein Mohammed Merza

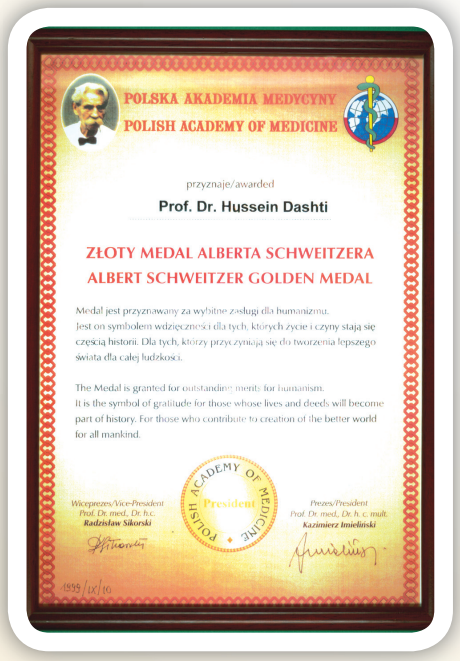
ختم المدرسة

نبذة عن حياة أ.د / حسين محمد دشتي في صور

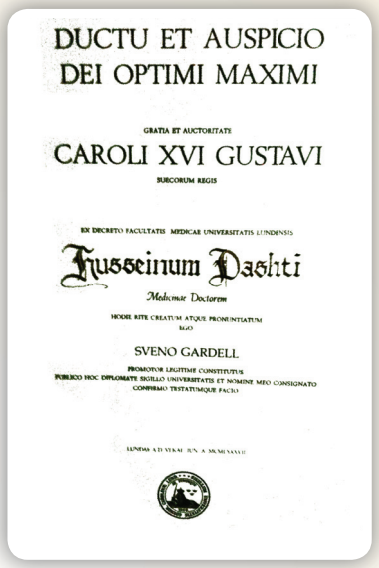
نبذة عن حياة أ.د / حسين محمد دشتي في صور







نبذة عن حياة أ.د / حسين محمد دشتي في صور



DUCTU ET AUSPICIO
DEI OPTIMI MAXIMI

GRATIA ET AUCTORITATE
CAROLI XVI GUSTAVI
SUECORUM REGIS

EX DECRETO FACULTATIS MEDICAE UNIVERSITATIS LUNDENSIS

Husseinum Dashti

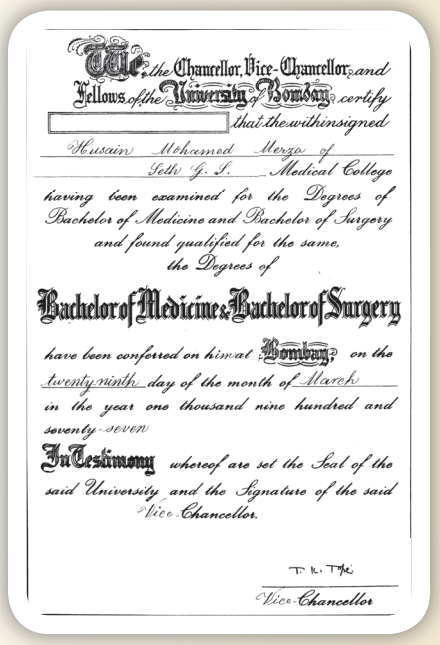
Medicinae Doctorem

HODIE RITE CREATUM ATQUE PRONUNTIATUM
EGO

SVENO GARDELL

PROMOTOR LEGITIME CONSTITUTUS
PUBLICO HOC DIPLOMATE SIGILLO UNIVERSITATIS ET NOMINE MEO CONSIGNATO
CONFIRMO TESTATUMQUE FACIO

LUNDAE A.D. VI KAL. JUN. A. MCMLXXVIII



The Chancellor, Vice-Chancellor, and Fellows of the University of Bombay, certify that the withinsigned

Husain Mohamed Merza of
Seth G. S. Medical College

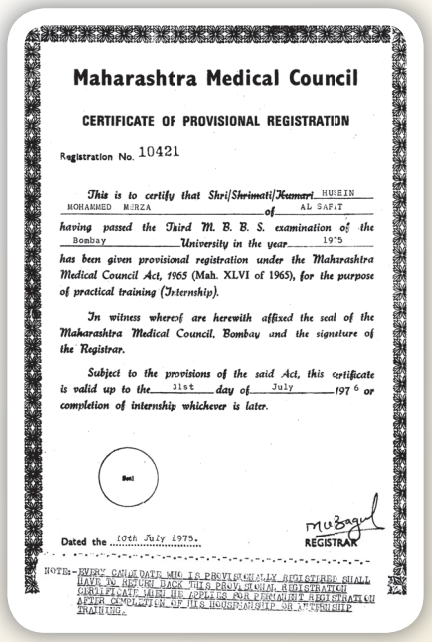
having been examined for the Degrees of Bachelor of Medicine and Bachelor of Surgery and found qualified for the same, the Degrees of

Bachelor of Medicine & Bachelor of Surgery

have been conferred on him at Bombay on the twenty-ninth day of the month of March in the year one thousand nine hundred and seventy-seven

In Testimony whereof are set the Seal of the said University and the Signature of the said Vice-Chancellor.

T. K. Tope
Vice-Chancellor



Maharashtra Medical Council

CERTIFICATE OF PROVISIONAL REGISTRATION

Registration No. 10421

This is to certify that Shri/Shrimati/Kumari HUSEIN MOHAMMED MERZA *of* AL SAFIT *having passed the Third M. B. B. S. examination of the* Bombay *University in the year* 19'5 *has been given provisional registration under the Maharashtra Medical Council Act, 1965 (Mah. XLVI of 1965), for the purpose of practical training (Internship).*

In witness whereof are herewith affixed the seal of the Maharashtra Medical Council, Bombay and the signature of the Registrar.

Subject to the provisions of the said Act, this certificate is valid up to the 31st *day of* July 197 6 *or completion of internship whichever is later.*

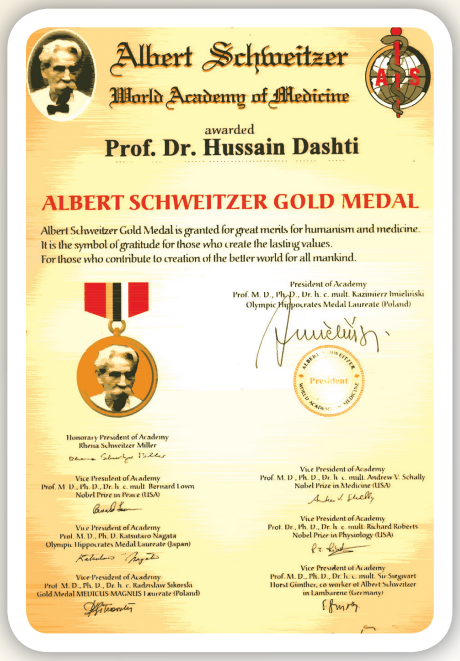
Seal

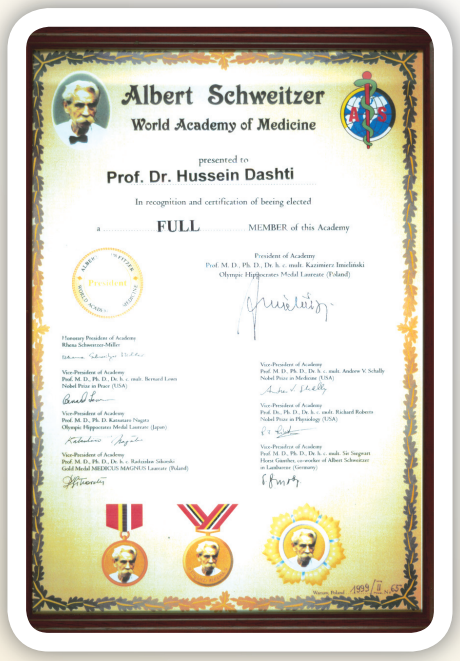
Dated the 10th July 1975.

REGISTRAR

NOTE:- EVERY CANDIDATE WHO IS PROVISIONALLY REGISTERED SHALL HAVE TO RETURN BACK THIS PROVISIONAL REGISTRATION CERTIFICATE AFTER COMPLETION OF HIS INTERNSHIP OR APPRENTICESHIP TRAINING.

نبذة عن حياة أ.د / حسين محمد دشتي في صور





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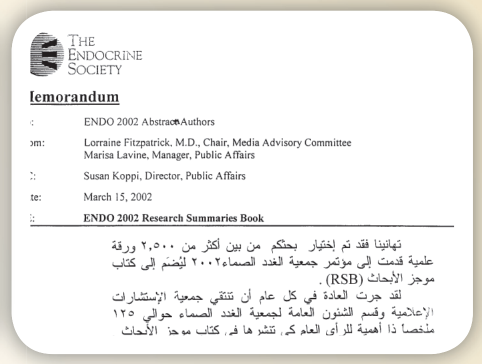

The Endocrine Society

Iemorandum

: ENDO 2002 Abstract Authors

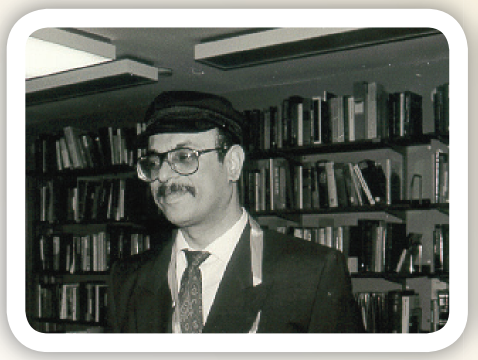
om: Lorraine Fitzpatrick, M.D., Chair, Media Advisory Committee
Marisa Lavine, Manager, Public Affairs

: Susan Koppi, Director, Public Affairs

te: March 15, 2002

: **ENDO 2002 Research Summaries Book**

تهانينا فقد تم إختيار بحثكم من بين أكثر من ٢,٥٠٠ ورقة علمية قدمت إلى مؤتمر جمعية الغدد الصماء٢٠٠٢ ليُضم إلى كتاب موجز الأبحاث (RSB) .
لقد جرت العادة في كل عام أن تنتقي جمعية الإستشارات الإعلامية وقسم الشئون العامة لجمعية الغدد الصماء حوالي ١٢٥ ملخصا ذا أهمية للرأي العام كي تنشر ها في كتاب موجز الأبحاث




من دون أدوية وبلا عمليات جراحية

علاج مرض السمنة بنظام غذائي صحي في كلية الطب في جامعة الكويت


جمعية دولية تختار بحثا كويتيا حول السمنة من بين ٢٥٠٠ بحث

الكويت – كونا – اختير بحث طبي كويتي حول تقليل وزن الجسم لدى مرضى السمنة من بين ٢٥٠٠ بحث في المؤتمر العالمي لجمعية (اندوكرين سوسايتي) للغدد الصماء الذي عقد في مدينة سان فرانسيسكو بالولايات المتحدة الاميركية مؤخرا.

وقال الاستاد في كلية الطب بجامعة الكويت الدكتور حسين دشتي في حديث لوكالة الانباء الكويتية (كونا) ان البحث المقدم من دولة الكويت في المؤتمر العالمي الذي حضره مع زميله الدكتور ناجي سعود الزيد تم اختياره ضمن اربعة بحوث اخرى للنشرة الصحفية للمؤتمر، واصفا ذلك بانه انجاز كبير يسجل لصالح جامعة الكويت الدولية في مجال الطب.

واوضح ان البحث الذي شارك فيه نخبة من الاساتذة، وهم الدكتور عبدالله بهبهاني والدكتور سامي اصفر والدكتور هلال الساير والدكتور موسى

يستفيد من الطاقة بصورة اكبر ويزيد من نشا... بشكل افضل.

وقال ان من الامور المبهرة في اتباع نظام الحمية الكيتونية لتقليل الوزن الذي تستغرق مدته اسبوعين الى اربعة اسابيع هي عمله في خفض م... التريجلايسليد (الدهون الثلاثية) واجم... الكوليسترول والكوليسترول السيئ والجلوكوز حين يزداد معدل الكوليسترول الجيد في الجسم ... المرضى.

وذكر الدكتور دشتي ان الدراسة لهذا البـ... استغرقت ١٢ اسبوعا وشملت ٦٣ مريضا بالسـ... حيث كانت نسبة الاناث الى الذكور اثنين الى واـ... مبينا ان الدراسة اظهرت سلامة وفعالية نظام الحـ... عن الدهون العالية وانه نظام امن لمعالجة السـ... ويمكن ان يعمل به كقياس واجراء وقائي ضد الـ...


شهادة تقدير

قم للمعلم وفيه التبجيلا ... كاد المعلم أن يكون رسولاً

إلى الأستاذ الدكتور / حسين دشتي

رئيس قسم التشريح في كلية الطب

إلى من أعطى من عمره فأجزل .. وعمل فأجاد .. وعلم فأفاد

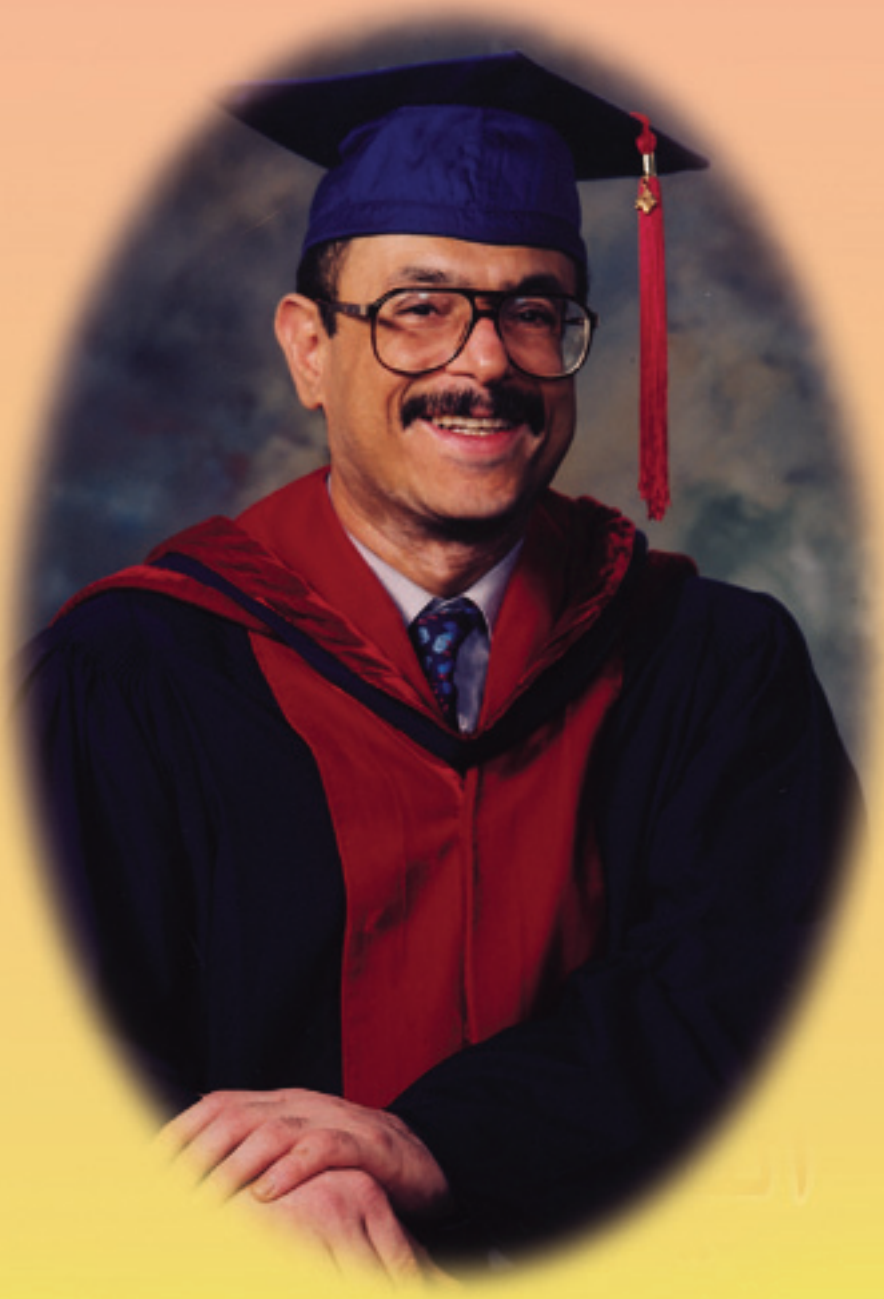
وغرس فأحسن .. وصادق فأخلص .. وكان الحصاد أجيالا

ستذكره دائما بكل خير وذكرى طيبة في القلوب والعقول ستظل

فواحة العبير مادام في الأبدان أرواح تسير ودماء تجري،،،

عن طلبة وطالبات دفعة 2000
وبتمثيله
فهد المزيدي & حسين الشباز

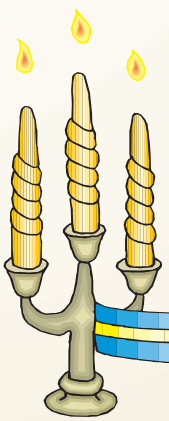
عميد كلية الطب
الأستاذ الدكتور
عبد الله بهبهاني



السيـــرة الذاتيـــة

أكلما رُمت جيشاً فانثنى هرباً ... تصرفت بك في آثاره الهمم
عليك هزمهم في كل معترك ... وما عليك بهم عار إذا انهزموا
أما ترى ظفراً حلواً سوى ظفرٍ ... تصافحت فيه بيض الهند واللمم
يا أعدل الناس إلا في معاملتي ... فيك الخصام وأنت الخصم والحكم
أعيذها نظراتٍ منك صادقةً ... أن تحسب الشحم فيمن شحمه ورم
وما انتفاع أخي الدنيا بناظره ... إذا استوت عنده الأنوار والظلم
أنا الذي نظر الأعمى إلى أدبي ... وأسمعت كلماتي مَن به صمم
أنام ملء جفوني عن شواردها ... ويسهر الخلق جرّاها ويختصم
وجاهلٍ مدّه في جهله ضحكي ... حتى أتته يد فرّاسة وفم
إذا نظرت نيوب الليث بارزةً ... فلا تظنن أن الليث مبتسم
ومهجة مهجتي من هم صاحبها ... أدركتها بجواد ظهره حرم
رجلاه في الركض رجل واليدان يد ... وفعله ما تريد الكف والقدم
ومرهفٍ سرت بين الجحفلين به ... حتى ضربت وموج الموت يلتطم
فالخيل والليل والبيداء تعرفني ... والسيف والرمح والقرطاس والقلم
صحبت في الفلوات الوحش منفرداً ... حتى تعجّب مني القور والأكم
يا من يعزّ علينا أن نفارقهم ... وجداننا كل شيء بعدكم عدم

● المتنبي



السيرة الذاتية (مختصرة)
أ . د حسين محمد دشتي

● **المركز الحالي :** بروفيسور قسم الجراحة – كلية الطب – جامعة الكويت .
: رئيس قسم التشريح – كلية الطب – جامعة الكويت

● الاختصاص والاختصاصات الدقيقة:

١- أستاذ جراحة – كلية الطب – جامعة الكويت
٢- تخصص رفيع في المعادن النادرة
٣- عضو الجمعية الطبية الكويتية
٤- باحث علمي بجامعة لوند بالسويد
٥- عضو مؤسس في الجمعية الدولية عن المعادن النادرة في جسم الانسان
٦- عضو مؤسس اللجنة الأفروآسيوية المنظمة لهيئة التقدم في البحوث عن المعادن النادرة في جسم الإنسان.
٧- عضو الهيئة الأوربية للأبحاث في مجال الجراحة.

● **الشهادات:**

١- بكالوريوس طب وجراحة ١٩٧٥ جامعة بومباي (الهند)
٢- دكتوراه في الطب جامعة لوند ١٩٨٦ السويد.
٣- زميل كلية الجراحين العالمية.
٤- زميل كلية الجراحين الأمريكية.

● **الجوائز والميداليات:**

١- حاصل على الجائزة والميدليات الذهبية من جامعة كاستربا في مجال البحث عن السرطان سنة ١٩٩٦ .
٢- جائزة أحسن بحث علمي من سويسرا لعلاقة المعادن (الزنك) بالعقم سنة ١٩٩٨.
٣- جائزة الإنتاج العملي من مؤسسة الكويت للتقدم العلمي سنة ١٩٩٤.
٤- حاصل على جائزة ألبرت شوايتزر في العلوم الطبية مايو سنة ١٩٩٩.
٥- حاصل على جائزة من الأكاديمية العالمية مايو سنة ١٩٩٩.

٦- حاصل على جائزة ألبرت شوايتزر الطبية الذهبية رفيعة المستوى المنوحة إليه من قبل الأكاديمية البولندية والعالمية للعلوم الطبية لتعمقه في الأبحاث وإنسانيته في مجال الطب نوفمبر سنة ١٩٩٩.
٧- حاصل على جائزة أفضل بحث علمي عن الغذاء الكيتوني ٢٠٠٤ كلية الطب.
٨- حاصل على جائزة التمييز في الطب والصحة من مجال (العصر) ١٦ نوفمبر ٢٠٠٥.

● **الخبرة والأنشطة:**

١- تخرج من جامعة بومباي سنة ١٩٧٥.
٢- دكتوراة من جامعة لوند بالسويد.
٣- عمل طبيباً جراحاً في مستشفى الأميري سنة ١٩٧٥.
٤- مسجل في قسم الجراحة سنة ١٩٧٧.
٥- مدرس في جامعة الكويت سنة ١٩٨٨ - قسم الجراحة.
٦- أستاذ مساعد في سنة ١٩٩٣ - كلية الطب - قسم الجراحة.
٧- عميد مساعد للشؤون الإدارية والمالية ٩٤ ١٩٩٨.
٨- استشاري جراحة سنة ١٩٩٤.
٩- عميد مساعد للشؤون الإدارية والمالية ١٩٩٨- ٢٠٠٢.
١٠- رئيس المجلة الطبية الكويتية منذ يناير ٢٠٠١- - ديسمبر ٢٠٠٥.
١١- بروفيسور في قسم الجراحة - كلية الطب منذ ١٩٩٧.
١٢- رئيس قسم التشريح - كلية الطب - جامعة الكويت.
١٣- نائب الاكاديمية العالمية ٢٠٠٨

July - 1988-1993	Senior Registrar, Surgical Unit, Salmiya Clinic.
Feb. - 1988-1993	Assistant Professor, Department of Surgery, Faculty of Medicine, Kuwait University.
April 1993-1997	Associate Professor, Department of Surgery, Faculty of Medicine, Kuwait University.
June 1997	Professor, Department of Surgery, Faculty of Medicine, Kuwait University.

C. <u>CLINICAL WORK IN THE PRESENT POSITION :</u>

April 1993 - Present	Consultant Surgeon, Salmiya Clinic.

3. ACADEMIC RECORD:

A. PRESENT POSITION:

A. Vice-Dean Administration,	Faculty of Medicine, Kuwait University - 8/10/94
B.Associate Professor, Faculty of Medicine, Kuwait University	Department of Surgery, April 1993-1997
C. Consultant Surgeon	Surgical Department Salmiya Clinic, Kuwait -April 1993
D. Head of Research Hawaly District,	Health Department, Ministry of Public Health. - May 1990
E.Chairman	Department of Surgery Faculty of Medicine - 1996 – 1998
F.Professor	Department of Surgery, Faculty of Medicine, Kuwait University -June 1997
G. Vice-Dean Administration & Finance	Faculty of Medicine, Kuwait University January 2001 - present

B. PROFESSIONAL EXPERIENCE

1975 - 1977 House Resident, Kuwait Training Programme.

A. General Surgery 6 months (Amiri Hospital).
B. General Medicine ٦ months (Sabah Hospital).
C. Paediatric 3 months (Sabah Hospital).
D. Psychiatric ٣ months (Psychiatric Hospital).
E. Gynaecology & Obstetric 6 months (Sabah Hospital)

1977 - 1979 Assistant Registrar in Surgery (Amiri) Hospital).
Jan.1979 - Nov. 1982 Registrar in Surgery (Amiri & Farwaniya) Farwaniah).
Jan.1987 - Feb. 1988 Registrar (Farwaniah Hospital).
Feb.1988 Acting Senior Registrar, Surgical Department, Salmiya Clinic.

2. ACADEMIC QUALIFICATIONS :

A. EDUCATION:

1.	M.D., Ph.D.	University of Lund, Sweden December 1986.
2.	M.B., B.S.	G.S. Medical College, Bombay University, Bombay, India. April 1975.
3.	F.I.C.S.	Fellow of International College of Surgeons Chicago, U.S.A. October, 1989.
4.	F.A.C.S.	Fellow of the American College of Surgeons Chicago, U.S.A. September, 1995.

B. FIELD OF SPECIALIZATION :

Structural and Functional studies of the liver diseases with special references to surgical aspects. (Clinical and Experimental approach).

ملخص السيرة الذاتية باللغة الإنجليزية

CURRICULUM VITAE

PROF. HUSSEIN DASHTI
MD., Ph.D., FICS., FACS

Department of Surgery
Faculty of Medicine
Kuwait University
P.O.Box 24923,
13110 Safat
Kuwait.

الأبحاث المنشورة في المجلات الطبية المحكمة

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الأبحاث المنشورة للدكتور حسين دشتي من عام ١٩٨٣ - ٢٠١٠ م

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اللهم إني أعتذر إليك من مظلوم ظُلِمَ بحضرتي فلم أنصره، ومن معروف أُسْدِيَ إلي فلم أشكره، ومن مسيءٍ اعتذر إليّ فلم أعذره، ومن ذي فاقة سألني فلم أُؤثره، ومن حق ذي حق لزمني لمؤمن فلم أوفره، ومن عيب مؤمن ظهر لي فلم أستره، ومن كل إثم عرض لي فلم أهجره، أعتذر إليك يا إلهي منهن ومن نظائرهن اعتذار ندامة يكون واعظاً لما بين يدي من أشباههن، فصلّ على محمد وآله واجعل ندامتي على ما وقعت فيه من الزلات وعزمي على ترك ما يعرض لي من السيئات توبة توجب لي محبتك يا محب التوّابين.

الإمام علي بن الحسين
زين العابدين (ع)

النظام الغذائي
لعلاج الأمراض المتعلقة بالسمنة

الفصل الثاني

ابحاث أ.د/حسين دشتي
والمقالات المنشورة في
المجلات الطبية المحكمة

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an increase in lipogenesis, rather than oxidation, leading to fat deposition and obesity.

Several mechanisms are involved in the reduction of body weight using LCKD. There is a greater loss of glycogen and water in this diet compared to the other diets that leads to an initial rapid weight loss. This occurs during the depletion of glycogen storage as each gram of glycogen is stored in 3 g of water (Kreitzman et al., 1992). Also, due to ketosis, there is energy loss in the form of ketones in urine, sweat or feces. Ketones have a diuretic effect and therefore lead to an even greater water loss, which has been measured from 4.5 to 15 lbs (Phinney et al., 1983). Further reduction in weight results from thermogenesis and increased fat loss, with preserved lean body mass (Willi et al., 1998). In contrast to our results other investigators (Kettelhut et al., 1980; Siegel et al., 1980) showed an increase in the body weight of LCKD fed rats. However, the LCKD composition used in these studies were different from what we used in our studies.

Consumption of high glycemic index diet (ND and HCD) was associated with a higher risk of diabetes (Hodge et al., 2004). However, the results presented here shows that STZ injected LCKD group showed no substantial change in the blood glucose level and remained within the normal range of 100 mg/dL. Previous studies from other investigators have also shown the protective effect of high-protein, CHO-free diet in the induction of diabetes using STZ (Eizirik and Migliorini, 1984; Eizirik et al., 1985). They found that rats adapted to a high-protein, CHO-free diet for period of 15–21 days prior STZ injection, showed decrease in the severity of diabetes and reduced the diabetogenic effect of STZ.

Although the LCKD group showed the least food intake and body weight gain comparing to other groups, all the diets used were approximately isocaloric. This is believed to be due to regulation of food intake through the action of a number of peptides. One of them is cholecystokinin (CCK), which is a satiation signal that is released predominantly from I-cells in the small intestine in response to the presence of fat or protein, which have a high satiety value (Kerstens et al., 1985). Plasma CCK concentrations are elevated in response to fat digestion, not by carbohydrates digestion (Torregrossa and Smith, 2003).

Other peptides that affect food intake are peptide YY (PYY), neuropetide Y (NPY) and leptin. PYY is shown to reduce food intake in high-fat fed rodents and also elevate fat oxidation (Adams et al., 2006). On the other hand, leptin can modulate energy expenditure, appetite and sympathetic nervous activity (Haynes, 2005). It can directly inhibit NPY and enhance melanocortin action which is responsible for suppression of feeding, which means that leptin can promote weight loss (Haynes, 2005).

Beside these peptides, ketone bodies in LCKD also play a role in the regulation food intake. In a study involving 3-hydroxybutyrate (3-OHB) infusions in Sprague–Dawley and Osborne–Mendel rats, which were fed low-fat or high-fat diets, it has been found that both groups exhibited reduced food intake and body weight, indicating that increased circulating levels of 3-OHB act as a satiety signal (Arase et al., 1988).

After STZ injection, the diabetic groups of ND and HCD showed polyphagia as expected while the food intake remained constant in LCKD group, which was in agreement with the studies of other investigators (Yancy et al., 2004). Also, polydipsia was observed in diabetic rats that were fed with normal and high carbohydrate diet, but the water intake of LCKD diabetic rats remained constant. Similarly, rats fed on ND and HCD showed a significant increase in urine output and the STZ injected rats fed on LCKD did not show a significant increase in urine output. In support to the data presented in this study, other studies using CHO restricted diet (Schmidt et al., 1980) or CHO-free diet (Eizirik and Migliorini, 1984; Eizirik et al., 1985) also showed similar results in water intake, urine excretion and food consumption.

Urine glucose analysis showed the presence of glucose in ND-D and HCD-D groups while glucose was absent in the LCKD-D group. The presence of glucose in the urine also correlated with the polyurea condition in these groups since it has a diuretic effect (Shihabi et al., 2001).

In our studies, STZ injection showed a decrease in the number of β cells in rats belonging to the ND and HCD groups as demonstrated by other investigators (Lazarys and Shapiro, 1972; Mythili et al., 2004). However, there was no difference between LCKD control and diabetic groups as well as between LCKD control and control of ND and HCD. Based on these observations, we suggest that LCKD, specifically ketone bodies functions as antioxidants that prevent the diabetogenic effect of STZ. In this regard, it has been shown that inducing ketosis either by the administration ketone bodies or LCKD, elevates the antioxidative capacity in the central nervous system, and improves the conditions of patients with neurologic disorders (Peterson et al., 2005; Maalouf et al., 2007). Veech et al. (2001) also suggested that ketones might reduce oxidative stress in cardiac tissue. Nazarewicz and his colleagues (2007) found that ketone bodies, particularly beta-hydroxybutyrate, significantly increased the redox status of healthy human blood.

In conclusion, this study suggests that LCKD prevents the development of streptozotocin in duced diabetes and its complication in rats. However, further studies are necessary to understand the underlying cellular mechanisms. Further studies on the therapeutic role of LCKD in diabetes are in progress in our laboratory.

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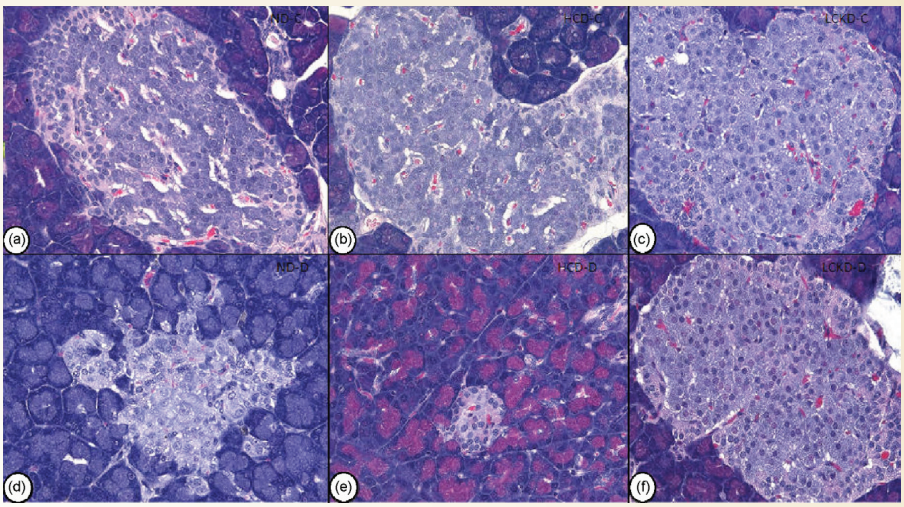

Fig. 8. Sections of the pancreas from control and diabetic rats of pre-fed experiment stained with Gomori's Chrome Alum Haematoxylin–Phloxine stain. β cells with blue and located interior, α cells with red found at periphery and δ cells pink to red located among α cells. Magnification 40×. (For interpretation of the references to color in the figure caption, the reader is referred to the web version of the article.)

(Fig. 7a and b). In the diabetic groups of ND and HCD, the islet morphology was altered with vacuoles and only a few islets were seen in the tissue sections (Fig. 7d and e). On the other hand, the islets were normal and intact in both the control and the diabetic group of LCKD (Fig. 7c and f). Gomori's Chrome Alum Haematoxylin–Phloxine stain was used to distinguish the endocrine cells of pancreas and to highlight the blue stained insulin producing β cells from the red α and the pink to red δ cells (Fig. 8). The data showed a decrease in the number of β cells in diabetic rats of ND and HCD with $p = 0.022$ and $p = 0.012$, respectively, compared to their control groups. There was no difference, however, between LCKD control and diabetic groups ($p = 0.981$) as well as between LCKD control and control of ND and HCD (Fig. 9).

5. Discussion

Diabetes mellitus (DM) is a common endocrine disorder worldwide and its occurrence continues to increase. It has been widely accepted that dietary components have a significant role in the clinical management of DM. Various studies from our laboratory have shown that ketogenic diet is effective in achieving weight loss and may have beneficial effects on glycemic control, triglyceride levels, and high-density lipoprotein cholesterol levels in diabetic patients. (Dashti et al., 2003, 2004, 2006, 2007). The results of the animal experiments presented in this study clearly shows that the rats fed on LCKD had remarkable tolerance to STZ and did not develop diabetes.

In this study, diabetes was induced in rats using STZ injection. STZ selectively destroys pancreatic β cells (insulin producing cells) by inducing DNA methylation and DNA damage, causing activation of poly(ADP-ribose) polymerase (PARP). This results in the reduction of cellular NAD^+, severe ATP depletion and eventually cell death (Bolzán and Bianchi, 2002). The rats on LCKD showed greater resistance to the diabetogenic action of the drug. This was proven by measuring the metabolic parameters, including changes in body weight, blood glucose, food and water intake and urine output.

The tendency to put on weight are higher in the normal and high carbohydrate diets fed animals as compared to LCKD. The mechanisms by which ND and HCD increase and LCKD reduce body weight were explained in several studies (Ludwig, 2002; Ebbeling et al., 2003). ND and HCD with high carbohydrate (CHO) contents, have high glycemic index. CHO is considered as the major stimulus for insulin secretion. This induces a more rapid insulin response which leads to a hypoglycemic postprandial period, that causes appetite stimulation and increase in caloric intake. Secondly, insulin is an anabolic hormone and with continued hyperinsulinemia there is

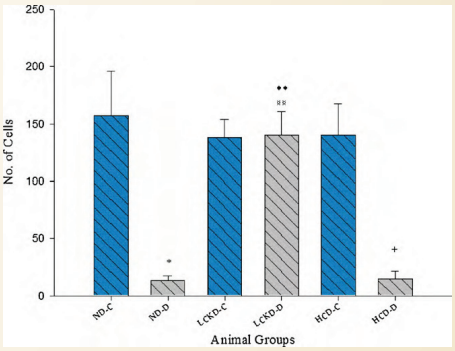

Fig. 9. The effect of different diets: normal diet (ND), high carbohydrate diet (HCD), and low carbohydrate ketogenic diet (LCKD) on number of β cells in control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). * = $p < 0.05$, ND-C compared to ND-D. + = $p < 0.05$, HCD-C compared to HCD-D. ♦♦ = $p < 0.01$, ND-D compared to LCKD-D. ♦♦ = $p < 0.01$, HCD-D compared to LCKD-D.

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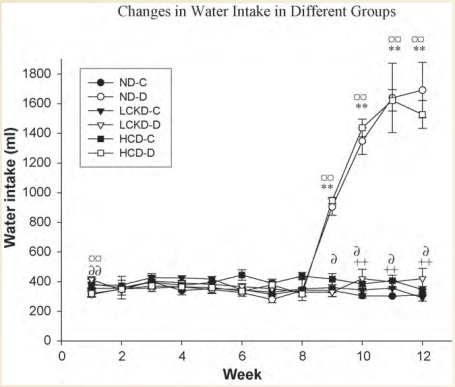

Fig. 5. The effect of different diet: normal diet (ND), high carbohydrate diet (HCD), and low carbohydrate ketogenic diet (LCKD) on water intake (mL) of control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). ** = $p < 0.01$, ND-C compared to ND-D. ++ = $p < 0.01$, ND-D compared to LCKD-D. ∂∂ = $p < 0.01$, HCD-D compared to LCKD-D. □□ = $p < 0.01$, HCD-C compared to HCD-D.

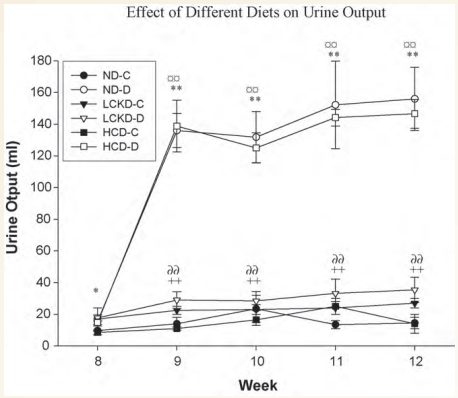

Fig. 6. The effect of different diet: normal diet (ND), high carbohydrate diet (HCD), and low carbohydrate ketogenic diet (LCKD) on urine output (mL) of control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). ** = $p < 0.01$, ND-C compared to ND-D. ++ = $p < 0.01$, ND-D compared to LCKD-D. ∂∂ = $p < 0.01$, HCD-D compared to LCKD-D. □□ = $p < 0.01$, HCD-C compared to HCD-D.

the experiment except for the diabetic ones (ND-D and HCD-D). There was a sudden increase in the urine output (polyurea) in the ND-D and HCD-D groups reaching about 165 mL/day at the end of the study (Fig. 6).

4.7. Effect of different diets on urine glucose level

The urine was tested for the presence of glucose, which is usually negative in normal conditions. Before week 8, all the groups showed negative glucosuria. After STZ injection, there was a significant appearance of glucose in the diabetic ND and HCD only, above 1000 mg/dL (past stage 4) indicating the development of a diabetic state. However, the diabetic group of LCKD continued to show negative glucosuria.

4.8. Histological assessment of islets of Langerhans

H&E staining showed the presence of several round to elongated islets distributed throughout the pancreas in all the control groups

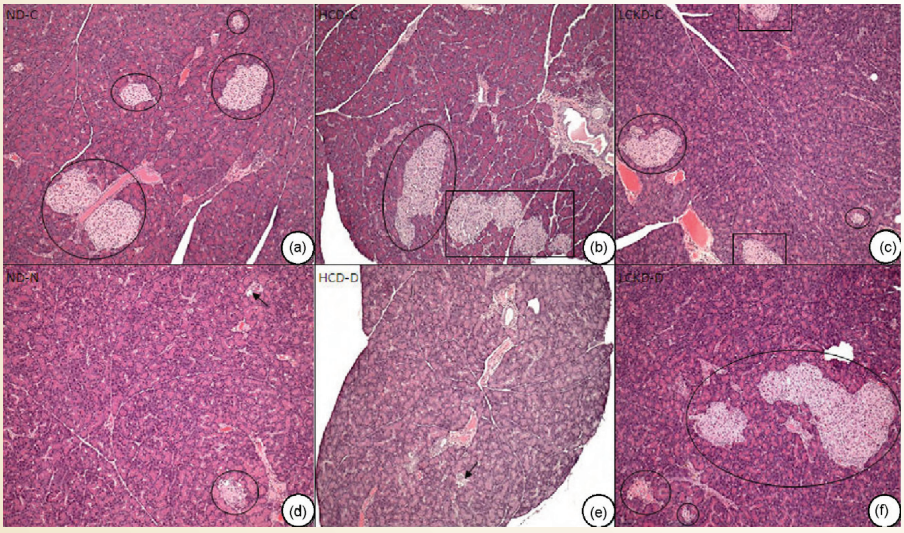

Fig. 7. Sections of the pancreas from control and diabetic rats of pre-fed experiment stained with H&E. Circles shows islets of Langerhans. Arrows shows vacuoles. Magnification 10×.

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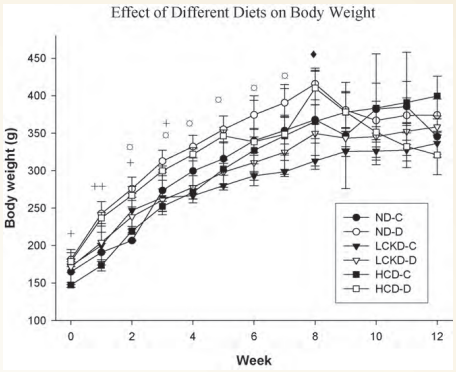

Fig. 1. Effect of different diets: normal diet (ND), high carbohydrate diet (HCD), and low carbohydrate ketogenic diet (LCKD) on body weight (g) in control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). ¤ = $p < 0.05$, ND-D compared to LCKD-D. ♦ = $p < 0.05$, HCD-D compared to LCKD-D.

intake comparing to the other groups. There was little increase in the food intake within the first 4 weeks, after that it decreased and remained constant during the whole experiment (Fig. 3).

4.4. Calories intake of different diet

The caloric content of the different diets was calculated form the combustion values for CHO, fats, and proteins, which are 4, 9 and 4 kcal/g, respectively. This amounted to 4.65 kcal/g in the ND, 4.5 kcal/g for HCD, and 5.5 kcal/g for LCKD. All the groups ingested about the same number of calories in the first few weeks until week 5. There was a significant increase in the caloric intake for ND and HCD compared to LCKD. This difference increased sharply with $p < 0.001$ after STZ administration in the diabetic groups of ND and HCD compared to LCKD-D as calorie intake was ranging between 600 and 800 kcal/g to reach up to 1600 kcal/g. This result was without subtracting the energy lost as urinary glucose or ketone bodies (Fig. 4).

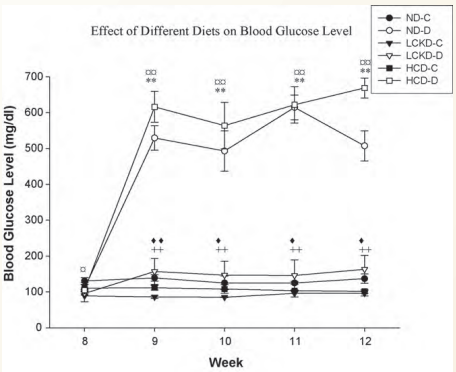

Fig. 2. The effect of different diets: normal diet (ND), high carbohydrate diet (HCD), and low carbohydrate ketogenic diet (LCKD) on blood glucose level (mg/dL) in control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). ** = $p < 0.01$, ND-C compared to ND-D. ++ = $p < 0.01$, ND-D compared to LCKD-D. ¤¤ = $p < 0.01$, HCD-C compared to HCD-D. ♦♦ = $p < 0.01$, HCD-D compared to LCKD-D.

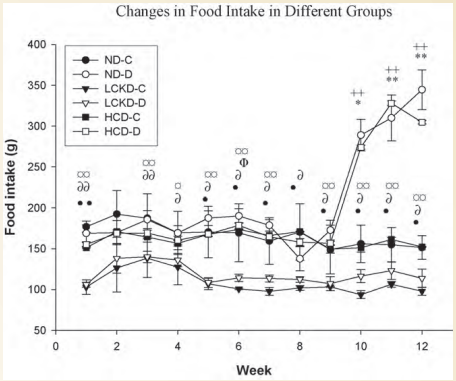

Fig. 3. The effect of different diets: normal diet (ND), high carbohydrate diet (HCD), and low carbohydrate ketogenic diet (LCKD) on food intake (g/week) in control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). * = $p < 0.05$, ** = $p < 0.01$, ND-C compared to ND-D. + = $p < 0.05$, ++ = $p < 0.01$, HCD-C compared to HCD-D. ∞ = $p < 0.05$, ∞∞ = $p < 0.01$, HCD-C compared to LCKD-C. ∂ = $p < 0.05$, ∂∂ = $p < 0.01$, HCD-D compared to LCKD-D. ¤ = $p < 0.05$, ¤¤ = $p < 0.01$, ND-D compared to LCKD-D.

4.5. Changes in water intake in different groups

In the first 8 weeks, there was no difference in water intake between the groups. However, after 8 weeks, as polydipsia is a characteristic feature of diabetes, the HD-D and HCD-D groups showed an increase in water intake. The LCKD-D group on the other hand showed a constant water intake throughout the experimental period (Fig. 5).

4.6. Effect of different diets on urine output

The amount of urine excreted was monitored weekly and it was between the range of 15 and 35 mL/day in all the groups throughout

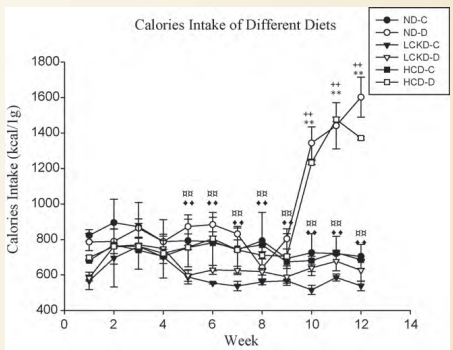

Fig. 4. The calories intake of different diets: normal diet (ND), high carbohydrate diet (HCD), and low carbohydrate ketogenic diet (LCKD) in control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). ** = $p < 0.001$, ND-C compared to ND-D. ++ = $p < 0.001$, HCD-C compared to HCD-D. ¤¤ = $p < 0.001$, ND-D compared to LCKD-D. ♦♦ = $p < 0.001$, HCD-D compared to LCKD-D.

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through methylation, the release of free radicals, or by the formation of nitric oxide (McNeill, 1999; Szkudelski, 2001). Due to these mechanisms, STZ is selectively cytotoxic to the β cells of pancreatic islets and a single intravenous or intraperitoneal injection of STZ (40–60 mg/kg body weight) can lead to type 1 diabetes in experimental animals (Bolzán and Bianchi, 2002). Using this molecule, hyperglycemia and insulin deficiency is provoked within 48 h of administration.

Although, a wide variety of drugs are used for diabetes management, there is still no satisfactory/effective therapy available for its cure. Furthermore, these drugs are either unaffordable due to socio-economic conditions or have undesirable side effects (Pari and Satheesh, 2004). It has been shown that changes in the dietary habits, especially a reduction in the carbohydrate content is quite effective and safer in diabetes management. The carbohydrate content of the diet is the most important factor that influences the glycemic level. Low carbohydrate diets appear to improve glycemic control and lessen the need for exogenous insulin and hypoglycemic medication (Arora and McFarlane, 2005). These diets have been found to significantly improve insulin sensitivity by up to 75% (Boden et al., 2005).

Low carbohydrate ketogenic diet (LCKD) is a diet that is low in carbohydrates (<100 g/day) causing ketosis, mimicking the physiological state of fasting (Freeman et al., 2006). It was first introduced as an epilepsy treatment at the beginning of the 20th century and with time LCKD became important in the treatment of several other conditions such as obesity, cardiovascular disease, and type 2 diabetes (Dashti et al., 2003, 2004, 2006, 2007; Freeman et al., 2006). This study, therefore, is aimed at investigating the protective role of LCKD in the development of diabetes in an experimental animal model of diabetes.

2. Materials and methods

2.1. Animals and experimental design

A total of 63 male Wistar rats, weighing 150–200 g, were used in this study. Animals were housed singly, under controlled environmental conditions of temperature 22.3 ± 0.3 °C, 31.2 ± 0.8% humidity, and a 12-h light/dark cycle in the Animal Care Facility at Kuwait University. This study was approved by the Animal Protection Ethical Committee of Kuwait University. The animals were divided into three groups: normal diet (ND) of regular commercial rat food (Mathew et al., 2006), Low carbohydrate ketogenic diet of 30% fat, 10% carbohydrate and 60% protein (LCKD), and high carbohydrate diet of 70% carbohydrate, 10% fat and 20% protein (HCD) as described previously (Al-Khalifa et al., 2009). Specific diets *ad libitum* were given to each group of animals for a period of 8 weeks. Each group was subdivided into normal control, sham control and diabetic groups. After 8 weeks, diabetes was induced using an intraperitoneal injection of STZ (S-0130, Sigma, Ronkonkoma, NY, USA), 55 mg/kg in saline, while the animals in the sham control group were given only saline.

On the day of injection, the blood glucose level was measured from the tail using a glucometer (One touch ultra, Lifescan, Tokyo, Japan; Ugochukwu and Figgers, 2006). For the first 48 h after STZ injection, the animals were kept in metabolic cages and development of diabetes was confirmed using Keto-Diabur test strips (Accu-chek, Roche, Selangor Darul Ehsan, Malaysia; McNeill, 1999). Daily measurements of food and water intake as well as weekly measurements of body weight were taken during the whole experiment. In addition, blood glucose level (diabetic ≥ 250 mg/dL; Ugochukwu and Figgers, 2006) and urine output were taken once a week starting from the 8th week till the end of the experiment at the 12th week.

3. Preparation of specimen

At the end of the 12th week, animals were sacrificed and the rat's abdomen was opened with a midline incision, where the pancreas was taken for histological analysis by routine H&E and Gomori's Chrome Alum Haematoxylin–Phloxine staining methods.

Gomori's Chrome Alum Haematoxylin–Phloxine stain was used to distinguish endocrine cells of the pancreas and to highlight insulin producing cells (β cells) from α and δ cells (Drury and Wallington, 1980) as previously described (Al-Khalifa et al., 2009). Briefly, the staining method is as follows. Sections fixed in 10% formalin were treated with Bouin's fluid for 16–24 h. The slides were then washed in tap water to remove picric acid and then treated for 1 min with and an equal mixture of 0.3% potassium permanganate and 0.3% sulphuric acid. The tissues were decolourized with 2–5% solution of sodium bisulphate and washed well in running water. The slides were then stained in haematoxylin solution for 15 min until β cells become deep blue and rinsed in water and differentiated in acid alcohol for about 1 minute to remove background staining. They were washed well for about 10 min in running tap water until the sections were clear blue. After that, the slides were stained in 0.5% aqueous phloxine for 5 min and rinsed in water. The slides were then treated with 5% phosphotungstic acid for 1 min, washed in running tap water for 5 min so that sections become red colour and differentiated in 95% alcohol. Finally, the slides were dehydrated, cleared and mounted with a cover slip using a mixture of distyrene (a polystyrene), a plasticizer (tricresyl phosphate), and xylen (DPX). The tissue sections were examined using a light microscope (Zeiss, Hamburg, Germany) and images were captured with a Zeiss digital camera using Axiovision software (Zeiss, Hamburg, Germany).

3.1. Statistical analysis

For statistical analysis of the data Student's *t*-test and analysis of variance with Bonferroni correction were performed. A value of $p < 0.05$ was considered to be significant for the comparisons between the animals fed the normal, high carbohydrate, and low carbohydrate ketogenic diets.

4. Results

4.1. Effect of different diets on body weight

In the first 8 weeks, the body weight increased gradually in all groups, but significantly higher in ND and HCD compared to LCKD groups. After administration of STZ, there was significant drop in body weight in both groups ND-D and HCD-D as a characteristic feature of diabetic status. While in the LCKD-D group the body weight remained increasing constantly (Fig. 1).

4.2. Effect of different diets on blood glucose level

The blood glucose level was measured weekly using a glucometer with the blood collected from the rat's tail. After the administration of STZ the blood glucose level in ND-D and HCD-D groups were increasing from 105 mg/dL upto 650 mg/dL at the end of study except in the LCKD-D group where the blood glucose level remained within the normal range of 100 mg/dL (Fig. 2).

4.3. Changes in food intake in different groups

The food intake was almost constant in ND and HCD groups in the first 8 weeks. After that, the diabetic groups ND and HCD were in a state of polyphagia. The LCKD groups showed the least food

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Low carbohydrate ketogenic diet prevents the induction of diabetes using streptozotocin in rats

A. Al-Khalifa[a], T.C. Mathew[b,*], N.S. Al-Zaid[c], E. Mathew[a], H. Dashti[d]

[a] Department of Anatomy, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait
[b] Department of MLS, Faculty of Allied Health Sciences, Health Sciences Center, Kuwait University, Kuwait
[c] Department of Physiology, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait
[d] Department of Surgery, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait

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ABSTRACT

Diabetes continues to be an overwhelmingly prevalent endocrine disorder that leads to several micro- and macrocomplications. It has been widely accepted that changes in dietary habits could induce or prevent the onset of diabetes. It is shown that low carbohydrate ketogenic diet (LCKD) is effective in the amelioration of many of the deleterious consequences of diabetes. However, its role in preventing the onset of diabetes is not understood. Therefore, this study is focused on the effect of LCKD in preventing the induction of diabetes using streptozotocin (STZ) in rats by biochemical and histological methods. Forty-two Wistar rats weighing 150–250 g were used in this study. The animals were divided into three groups: normal diet (ND), low carbohydrate ketogenic diet (LCKD), and high carbohydrate diet (HCD). Specific diets *ad libitum* were given to each group of animals for a period of 8 weeks. Each group was further subdivided into normal control, sham control and diabetic groups. Animals in the diabetic group were given a single intraperitoneal injection of STZ (55 mg/kg). All the animals were sacrificed 4 weeks after the injection of STZ. Daily measurements of food and water intake as well as weekly measurement of body weight were taken during the whole 12 weeks of the experiment. After injecting with STZ, the blood glucose level of all the groups increased significantly except for the group fed on LCKD (p value < 0.01). Also, food intake, water intake and urine output were significantly increased in all groups except for the LCKD group (p value < 0.01). There was also a significant decrease in the weight gain of the animals that were fed on a LCKD as compared to other groups (p value < 0.05). Although, substantial decrease in the number of β cells was noticed in diabetic rats, there were no change in the number of β cells in the LCKD treated diabetic animals as compared to LCKD control group. The results presented in this study, therefore, suggests that LCKD prevents the development of diabetes using streptozotocin in rats.

1. Introduction

Diabetes mellitus (DM) is characterized by hyperglycemia which results from the defects in insulin secretion and/or insulin action. It is one of principal cause of morbidity and mortality in human population due to the development and progression of micro- and macrovascular complications including neuropathy, nephropathy, cardiovascular and cerebrovascular diseases (Altan, 2003). It has been estimated that diabetic patients exceed over 200 million worldwide and its prevalence is rapidly increasing (Malecki, 2004). Similarly, in the Gulf region, especially in Kuwait, diabetes is widely spreading and is considered as a major health problem (Abdella et al., 1999).

Several chemical agents can alter β-cell function leading to diabetes. One important chemical agent which can cause diabetes in experimental animals is streptozotocin (STZ). STZ is produced by *Streptomycetes achromogenes* and was originally identified as an antibiotic (Lewis and Barbiers, 1960). It is composed of a glucose molecule with a nitrosourea side chain. Upjohn Laboratories accidentally discovered that STZ could produce hyperglycemia, but the exact mechanism was not known until it was described how a single dose of streptozotocin (STZ) in dogs and rats can lead to β-cell death and results in the diabetic state (McNeill, 1999).

The glucose moiety of STZ binds to the glucose transporter GLUT2 present on the pancreatic β-cell membrane and enters the cell while the nitrosourea moiety is the part responsible for its cytotoxic effects. After STZ enters the β cells, cell death can occur

* Corresponding author at: Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Kuwait University, P.O. Box 31470, 90805 Sulaibikhat, Kuwait. Tel.: +965 24984875.
E-mail address: tcmkwt@gmail.com (T.C. Mathew).

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and a standard control diet in subjects with type 2 DM, it was shown that both diabetic-specific diets produced significantly lower blood glucose and insulin responses and higher levels of glucagonlike peptide-1 as compared with the standard diet [43].

Urine glucose and other analysis

Urine analysis showed that the glucose level in the ND-D and HCD-D was above 1000 mg/dL throughout the experimental period. However, in the LCKD-D group, high-level glucose was present only during the first 3 wk. Thereafter, the level of glucose in the urine of the LCKD-D group became almost normal. These results further suggest the beneficial effects of LCKD in the regulation of diabetes. Levels of ketones and proteins in the urine of experimental rats were consistent with the diabetic state of the animals.

Histologic assessment of the islets of Langerhans

Histologic studies showed a decrease in the number of islets as well as the number of β cells in all diabetic groups as compared with their respective controls. The histologic changes observed in this study correspond to the ultrastructural changes observed in the islets of Langerhans of mice in response to STZ [44]. Electron microscopic observation revealed early chromatin aggregation and cytoplasmic vesiculation in the central β cells during the first 2 h of STZ treatment. In addition, nuclear shrinkage and pyknosis with swelling of mitochondria and endoplasmic reticulum were observed [44]. Lysis of β cells occurred after 12 h of treatment. However, other cell types of the islets of Langerhans did not show any ultrastructural alteration. Macrophage infiltration and the presence of clear and large phagocytic vacuoles were observed among lytic β cells after 24 h of STZ administration. No features of apoptosis were observed, and the pancreatic tissue remained unaffected from the effect of STZ [44].

As shown by the metabolic parameters studied, during 8 wk of this experiment, diabetic rats on ND and HCD maintained a high glucose level throughout the experiment; in contrast, LCKD maintained the blood glucose level at near normal levels. These results are similar to the studies of other investigators [45,46] who used a low-carbohydrate diet in the treatment of diabetes. Recently various studies have been carried out on glycated hemoglobin (HbA_{1c}), which is considered as an index of blood glucose control and the degree of oxidative stress in diabetes [47,48]. It has been shown that administration of LCKD decreases the level of glycated hemoglobin in diabetic patients [12,23], suggesting a reduction in the generation of reactive oxygen species and an improvement in the oxidative status. All these studies suggest that LCKD may play a beneficial role in the amelioration of oxidative stress in diabetic patients. In support of this view, Falk and his collaborators [49] have shown that ketone bodies function as antiinflammatory agents through the reduction of reactive oxygen species and increase of glutathione peroxidase activity. Furthermore, according to Freeman and associates [50], the anticonvulsant role of a ketogenic diet could be due to the antioxidant mechanisms activated by fatty acids and ketones.

In conclusion, the histologic and biochemical data presented in this study support the view that the LCKD has a significant beneficial effect on ameliorating the diabetic state and helping to stabilize hyperglycemia and could result in improved β-cell function. Although the underlying mechanism of this protective effect is not understood, it is possible that, as mentioned above, the LCKD (fatty acids and ketone bodies) may have a significant role in reducing oxidative stress in STZ-induced diabetes in rats. Therefore, the LCKD may be effective in diabetes management by improving glycemia and reducing the need for medication in patients with diabetes.

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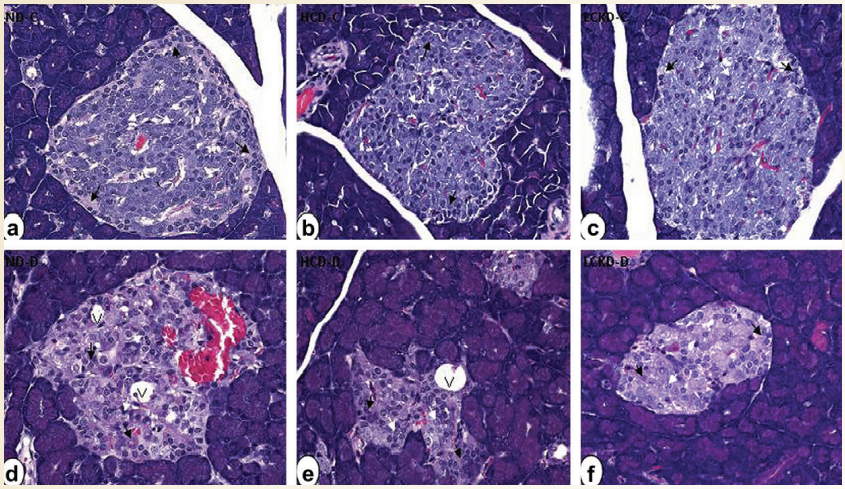

Fig. 6. Sections of the pancreas for control and diabetes rats of postfed experiment stained with Gomori's chrome alum hematoxylin-phloxine stain. Black arrows show α cells. White arrows show β cells. V, vacuoles. β cells with blue and located interior, α cells with red found at periphery, and δ cells pink to red are located among α cells. Magnification 40×.

Effect of diets on body weight and food intake

As expected with the diabetic condition, there was a significant ($P < 0.01$) reduction in the body weight and an increase in the food and caloric intake of the diabetic groups except for the LCKD group, confirming the beneficial effect of LCKD on the diabetic status. These results are similar to the studies of other investigators [36].

Effects of diets on water intake and urine output

As polydipsia and polyuria are conditions that are concomitant with the diabetic state, water intake and urine volume were markedly increased in the diabetic groups of ND and HCD. On the other hand, water intake in the LCKD-D group was within the normal range, whereas urine volume during the first 2 wk was considerably above the normal range due to glucose excretion. Gradually urine volume in the LCKD-D group returned to the normal level.

These results showing the general improvement in weight gain and polyuria condition were similar to the studies in which a low-carbohydrate diet [35–37] and carbohydrate-free diet [38] were used.

Contrary to our findings and other recent studies mentioned above, a few studies [39–42] showed that the low-carbohydrate, high-fat diet had worsened the diabetic state. Although the studies of Chisholm and O'Dea [42] were similar to our studies and the composition of LCKD and HCD used were similar, the exact reason why their results contradict the findings presented in this study is not understood. However, in a recent study evaluating the response of two lower-carbohydrate diets that were rich in slowly digested carbohydrate and monounsaturated and omega-3 fatty acids

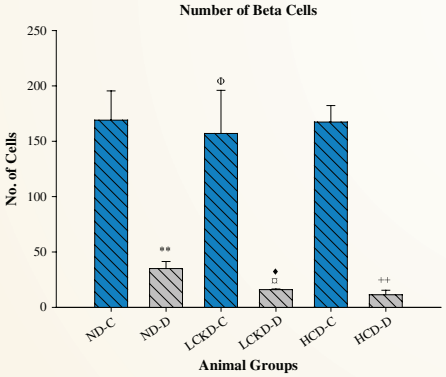

Fig. 7. The effect of different diet: normal diet (ND), high-carbohydrate diet (HCD), and low-carbohydrate ketogenic diet (LCKD) on number of β cells in control (C), and diabetic rats (D). The values are mean ± SEM ($n = 42$). **$P < 0.01$, ND-C compared with ND-D; ++, $P < 0.01$, HCD-C compared with HCD-D; ¤, $P < 0.05$, ND-D compared with LCKD-D; ◆, $P < 0.05$, HCD-D compared with LCKD-D; Φ, $P < 0.05$, LCKD-C compared with LCKD-D.

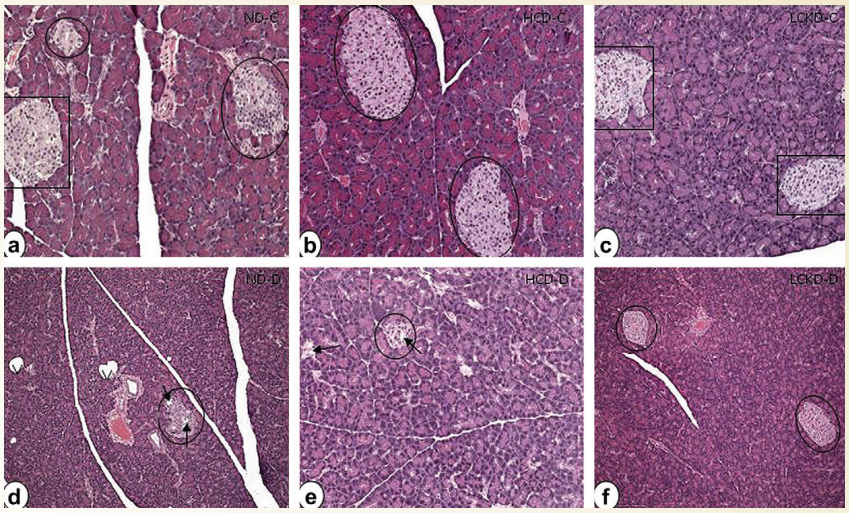

Fig. 5. Sections of the pancreas from control and diabetes rats of postfed experiment stained with hematoxylin and eosin. Circles show islets of Langerhans. Arrows show vacuoles. a, b, c and e: Magnification 20×; d and f: magnification 10×.

and only a few islets were present in tissue sections (Fig. 5). Furthermore, Gomori's chrome alum hematoxylin-phloxine staining showed the presence of only very few necrotic β cells in the islets. However, α and δ cells of the islets were not affected by STZ (Fig. 6). Macrophage infiltration and the presence of vacuoles were observed among lytic β cells. Statistical analysis showed a significant decrease in the number of β cells (Fig. 7) in all diabetic groups as compared with the respective control groups ($P < 0.01$).

Discussion

The data presented in this study clearly indicate the beneficial effects of LCKD in improving the diabetic status in terms of body weight, blood glucose, urine output, and food and water intake. In this study, after STZ injection, the rats were randomly assigned to the three diet groups to ensure that the results were due to the dietary effects rather than any other factors. Also, it is important to emphasize that this experiment was carried out without the usage of any hypoglycemic medication.

Effect of diets on blood glucose levels

After STZ administration, there was a significant increase in the blood glucose levels of all the diabetic groups as compared with their controls. However, the blood glucose level of the LCKD-D group was significantly lower ($P < 0.005$ and $P < 0.01$) than the other groups. As shown in Figure 2, there was a decrease in the blood glucose level in response to the LCKD diet from week 1, which reached almost normal levels (<200 mg/dL) at week 6. On the other hand, the rats assigned to the other two diets showed continuous increase in the blood glucose levels, reaching approximately 650 mg/dL. Therefore, the data presented in this study suggest that even short-term use of the LCKD has significant beneficial effects in STZ-treated diabetic rats. Several studies in which LCKD was administered in parallel with insulin and hypoglycemic medication, either for short or long periods, have shown the therapeutic effect of LCKD in improving the glycemic level as well as reducing the need for such medications [23–26]. This improvement in the glycemic level was achieved with a low-carbohydrate, high-protein diet [27,28] as well as with a low-carbohydrate, high-fat diet [29,30]. These studies suggest that reducing the amount of dietary carbohydrate is important in regulating diabetes. Moreover, our results on the metabolic improvement were similar when a 6% carbohydrate diet was given 11 days after the induction of diabetes [31], as well as with a carbohydrate-free diet given after 6 wk for spontaneously diabetic BB Wistar rats [32]. In 1990, Henry and his colleagues [33] showed that the improvement in the blood glucose levels is also due to the direct effect of the ketone bodies on the hepatic glucose output. Similarly, Müller and his colleagues [34] found that infusion of ketone bodies caused a decrease in hepatic glucose production, blood glucose, and glucose utilization.

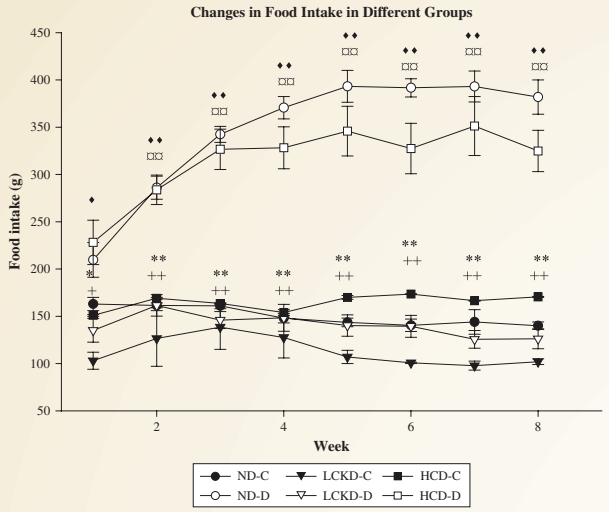

Fig. 3. The effect of different diets: normal diet (ND), high-carbohydrate diet (HCD), and low-carbohydrate ketogenic diet (LCKD) on food intake (g/wk) in control (C) and diabetic rats (D). The values are mean ± SEM (n = 42). ¤¤, $P < 0.01$, ND-C compared with ND-D; ◆, $P < 0.05$, ◆◆, $P < 0.01$, HCD-C compared with HCD-D; *$P < 0.05$, **$P < 0.01$, ND-D compared with LCKD-D; +, $P < 0.05$, ++, $P < 0.01$, HCD-D compared with LCKD-D.

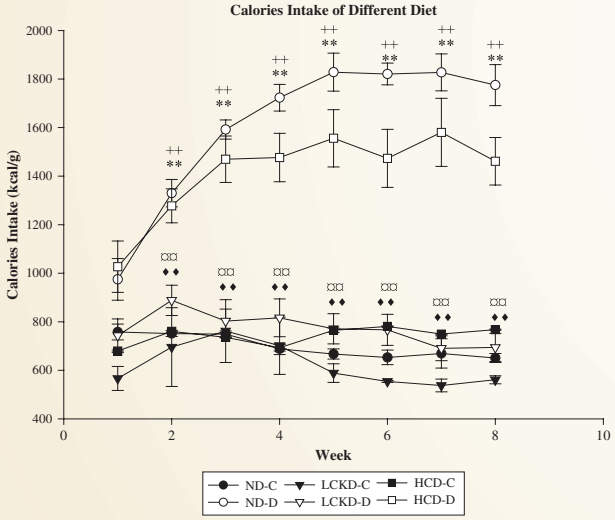

Fig. 4. The calorie intake of different diets: normal diet (ND), high-carbohydrate diet (HCD), and low-carbohydrate ketogenic diet (LCKD) in control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). **$P < 0.001$, ND-C compared with ND-D; +, $P < 0.05$, ++, $P < 0.01$, HCD-C compared with HCD-D; ¤¤, $P < 0.001$, ND-D compared with LCKD-D; ◆◆, $P < 0.001$ HCD-D compared with LCKD-D.

Changes in food intake in different groups

After STZ administration, as expected, the diabetic groups of ND and HCD showed an increase in food consumption. On the other hand, the LCKD groups showed the least food intake ($P < 0.01$) as compared with other groups (Fig. 3).

Calorie intake of different groups

All the control groups and LCKD-D ingested almost the same number of calories throughout the experiment. However, the diabetic groups of ND and HCD showed a significant ($P < 0.001$) high-calorie intake (Fig. 4).

Changes in water intake in different groups

The ND-D and HCD-D groups showed a significant increase ($P < 0.01$) in water intake as compared with the LCKD-D group throughout the experimental period.

Effect of different diets on urine output

Excretion of urine was monitored weekly. After STZ administration, there was a significant increase ($P < 0.01$) in the urine output in ND-D and HCD-D compared with their control groups and with LCKD-D. At the end of the study, the increase in urine output in the ND-D and HCD-D groups reached up to 250 mL/d. Although there was a slight difference in urine output between the control and diabetic groups of LCKD during the first few weeks, the urine excretion in the LCKD-D groups decreased constantly throughout the entire study period.

Effect of different diets on urine glucose and other analysis

The glycosuria was negative throughout the experiment in LCKD control (LCKD-C) and LCKD-D groups. In the LCKD-D group, trace to 250 mg/dL glucose was present during the first 3 wk. For the diabetic ND and HCD groups, there was a significant increase in the level of glucose in the urine (above 1000 mg/dL). Compared with LCKD-C, the control group of HCD showed trace to 250 mg/dL glycosuria during the whole experiment. Although urine did not show the presence of ketones in the normal state, the urine levels of ketones and proteins in the experimental rats were consistent with the diabetic state of the animals in different diet groups.

Histologic assessment of islets of Langerhans

Hematoxylin and eosin staining showed the presence of several round to elongated, normal islets of Langerhans in the control groups (Fig. 5). On the other hand, in all the diabetic groups, the islet morphology was altered with vacuoles

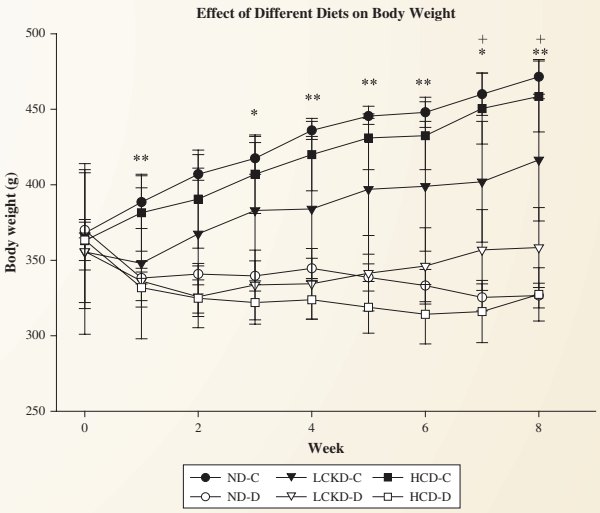

Fig. 2. Effect of different diets: normal diet (ND), high-carbohydrate diet (HCD), and low-carbohydrate ketogenic diet (LCKD) on body weight (g) in control (C) and diabetic rats (D). The values are mean ± SEM ($n = 42$). *$P < 0.05$, **$P < 0.01$, ND-C compared with ND-D; +, $P < 0.05$, ++, $P < 0.01$, HCD-C compared with HCD-D.

rinsed in water and differentiated in acid alcohol for about 1 min to remove the background staining. Again the slides were washed for 10 min in running tap water until the sections were clear blue. After that, the slides were stained in 0.5% aqueous phloxine for 5 min, rinsed in water, and then treated with 5% phosphotungstic acid for another min. The slides were washed in running tap water for 5 min so that sections became red and then differentiated in 95% alcohol. Finally, the slides were dehydrated, cleared and mounted with a cover slip using a mixture of distyrene (a polystyrene), a plasticizer (tricresyl phosphate), and xylene (DPX).

The tissue sections were examined using a light microscope (Zeiss, Hamburg, Germany) and images were captured with a Zeiss digital camera using Axiovision software (Zeiss, Germany).

Statistical analysis

The Student's *t* test and analysis of variance with Bonferroni correction were performed for the comparisons between animals fed the normal, high-carbohydrate, and low-carbohydrate ketogenic diets. A value of $P < 0.05$ was considered to be significant.

Results

There were no significant differences between the control group and the sham control for each diet group. Therefore, the control group and the sham control were combined to make the ''control'' group for each diet.

Effect of different diets on blood glucose level

The non-fasting blood glucose level was measured weekly from the tail vein of rats using a glucometer. After the administration of STZ, the blood glucose level was significantly increased in all diabetic groups compared with their control at all time points, except baseline. But the increase in the blood glucose level of LCKD diabetic (LCKD-D) group was significantly lower ($P < 0.005$ and $P < 0.01$) than the other diabetic groups. From the 6th wk onward, the blood glucose level of the diabetic groups of LCKD was almost similar to the control group (Fig. 1). Weekly comparison (using analysis of variance with Bonferroni correction) of LCKD-D with ND-D and HCD-D showed that starting from week 4 of the experiment, there were significant differences in the level of blood glucose between LCKD-D and ND-D as well as LCKA and HCD-D.

Effect of different diets on body weight

With STZ administration, there was a significant decrease ($P < 0.01$) in the body weight in both ND-D and HCD-D groups. On the other hand, there was no significant difference in body weight between the control and LCKD diabetic group (Fig. 2).

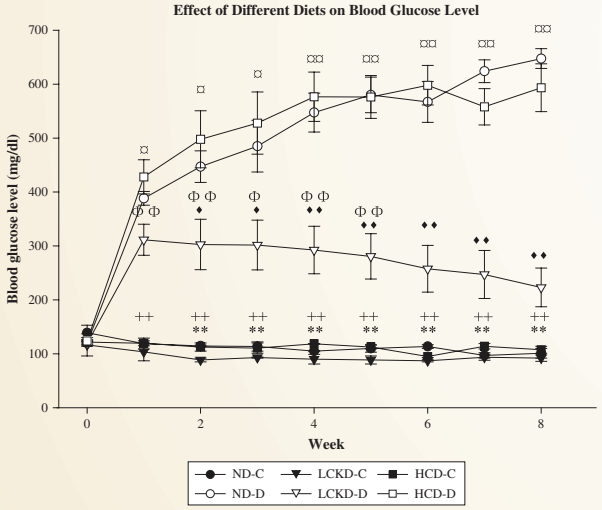

Fig. 1. The effect of different diets: normal diet (ND), high-carbohydrate diet (HCD), and low-carbohydrate ketogenic diet (LCKD) on blood glucose level (mg/dL) in control (C) and diabetic (D) rats. The values are mean ± SEM ($n = 42$). **$P < 0.01$, ND-C compared with ND-D; ++, $P < 0.01$, HCD-C compared with HCD-D; ¤, $P < 0.05$, ¤¤, $P < 0.01$, ND-D compared with LCKD-D; ♦, $P < 0.05$, ♦♦, $P < 0.01$, HCD-D compared with LCKD-D; Φ, $P < 0.05$, ΦΦ, $P < 0.01$, LCKD-C compared with LCKD-D.

DNA damage, severe adenosine triphosphate depletion, and eventually necrosis of the β cells [7]. Hence, a high dose of STZ severely impairs insulin secretion, mimicking type 1 diabetes [7]. However, specific STZ doses cause a partial destruction of β-cell mass. Therefore, administration of calculated doses of STZ can be used to produce type 2 DM [8]. But it is quite difficult to judge the appropriate dosage to create stable type 2 DM without either gradual recovery or deterioration into type 1 DM. STZ reliably produces many of the signs such as increased intake of water and food, failure to gain weight, and increased blood glucose concentrations and several symptoms of chronic human diabetes, in particular, diastolic cardiac dysfunction, cataracts, and neuropathy.

Maintaining blood glucose levels within the normal range is of utmost importance in the management of diabetes. Diet is one factor that can have a great impact upon stabilizing blood glucose levels in diabetic patients. Recent studies have reintroduced the concept of using a ketogenic diet with low-carbohydrate content in a variety of disease states, such as epilepsy [9], obesity [10], cardiovascular diseases [11], and diabetes [12].

A low-carbohydrate ketogenic diet (LCKD) is a high-fat, low-protein, low-carbohydrate ($<$100 g/d) diet that has been employed as a treatment for intractable epilepsy and obesity [13]. It consists of long-chain saturated triglycerides in a 3:1–4:1 ratio of fats to carbohydrates + protein (by weight). LCKD mimics the physiologic state of fasting [13].

It is generally believed that a high-fat diet causes obesity. As fat has a higher caloric density than carbohydrate, it is assumed that consumption of a high-fat diet will be accompanied by a higher energy intake [14]. On the contrary, current studies quite evidently show that a ketogenic diet can cure obesity [10] and obesity-associated diseases [11,12,15]. This concept that fat can be eaten ad libitum and still induce weight loss in obese subjects is actually quite old [16].

The extent of blood glucose level is determined by the amount and rate of glucose absorption from the gut and also by the rate of its utilization or storage when it enters the circulation [17]. In diabetes, as ingested carbohydrates are absorbed mainly as glucose, there is an immediate rise in the blood glucose level. The contents of an LCKD are mainly absorbed as triglycerides and proteins rather than glucose, so this would alleviate one of the major factors in diabetes.

Due to the above-mentioned reasons, this study is aimed at investigating the therapeutic effects of LCKD in diabetic rats as compared to normal and high-carbohydrate diets.

Materials and methods

Animals and experimental design

A total of 63 male Wistar rats, weighing 250–300 g, were used in this study. Animals were housed singly, under controlled environmental conditions of temperature 22.3 ± 0.3°C, 31.2 ± 0.8% humidity, and a 12-h light/dark cycle in the Animal Care Facility at Kuwait University. This study was approved by the Animal Protection Ethical Committee of Kuwait University.

The animals were randomly assigned to the three diet groups: (1) normal diet (ND) of regular commercial rat food [18]; (2) high-carbohydrate diet (HCD) of 70% carbohydrate, 10% fat, and 20% protein; and (3) LCKD of 60% fat, 10% carbohydrate, and 30% protein. Each group was further subdivided into three subgroups: control, sham, and diabetic rats (each group consisting of seven rats). All the groups had free access to water and food based on the type of diet. Each group of rats was fed with the specific type of diet for 8 wk.

Diabetes was induced first in rats by the intraperitoneal injection of STZ (S-0130, Sigma, Ronkonkoma, NY, USA), freshly prepared [19], at a concentration of 55 mg/kg in saline, and the animals in the sham control group were given only saline.

Before STZ injection, rats were caged singly in metabolic cages for 24 h to collect urine for analysis and for measuring the urine output. On the day of STZ injection, the level of blood glucose was measured from the rat tail using a glucometer (One touch ultra, Lifescan, Tokyo, Japan) [20]. After STZ injection and the development of diabetes, which was confirmed using Keto-Diabur test strips (Accu-chek, Roche, Selangor Daral Ehsan, Malaysia) [21], the animals were transferred into normal cages.

Daily measurements of food and water intake as well as weekly measurement of body weight were taken during the whole experiment. In addition, blood glucose level (diabetic $\geq$ 250 mg/dL) [20] and urine output were measured once a week.

Preparation of specimen

At the end of 8 wk, animals were anesthetized using ether, and blood was collected in vacutainer tubes (Vacutainer Brand, 5181548, BD Diagnostics, NJ, USA) by cardiac puncture. After the collection of blood samples, the animals were sacrificed, the abdomen opened with a midline incision, and the pancreas taken for histologic analysis by routine hematoxylin and eosin and Gomori's chrome alum hematoxylin-phloxine staining methods.

Gomori's chrome alum hematoxylin-phloxine stain was used to distinguish endocrine cells of pancreas and to highlight insulin-producing β cells from α and δ cells [22]. Briefly, the Gomori's chrome alum hematoxylin-phloxine staining method is as follows. Sections after their initial fixation in 10% formalin were treated with Bouin's fluid for 16–24 h. The slides were then washed in tap water to remove picric acid and then treated for 1 min with a mixture containing an equal amount of 0.3% potassium permanganate and 0.3% sulfuric acid. The tissues were decolorized with 2–5% solution of sodium bisulphate and washed well in running tap water. The slides were then stained with hematoxylin solution for 15 min until the β cells became deep blue. The slides were further

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Therapeutic role of low-carbohydrate ketogenic diet in diabetes

Alaa Al-Khalifa, M.Sc.[a], Thazhumpal Chacko Mathew, M.Sc., Ph.D., F.R.C.Path.,[a,b,*], Naji S. Al- Zaid, B.Sc., Ph.D.[d], Elizabeth Mathew, B.Sc.[a], and Hussein M. Dashti, M.D., Ph.D., F.I.C.S., F.A.C.S.[a,c]

[a]*Department of Anatomy, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait*
[b]*Department of M.L.S, Faculty of Allied Health Sciences, Health Sciences Center, Kuwait University, Kuwait*
[c]*Department of Surgery, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait*
[d]*Department of Physiology, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait*

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Abstract

Introduction: Changes in dietary habits influence the glycemic level. Preliminary studies using the low-carbohydrate ketogenic diet (LCKD) were found to be quite promising in controlling diabetes mellitus. Therefore, the objectives of this study are to investigate the therapeutic effects of LCKD in experimental diabetic rats following the administration of streptozotocin (STZ).

Materials and methods: Adult rats were divided into three groups: normal diet, LCKD, and high-carbohydrate diet. Each group was subdivided into normal, sham, and diabetic groups. Diabetes was induced by a single intraperitoneal injection of STZ (55 mg/kg). Specific diets were given to each group of animals for a period of 8 wk and then the animals were sacrificed. The rats were monitored daily for food and water intake, whereas body weight, urine output, and blood glucose levels were monitored weekly. The histology of the islets of Langerhans was studied by histochemical methods.

Results: The results showed that LCKD was effective in bringing blood glucose level close to normal ($P < 0.01$). Food and water intake and urine output were increased in all groups except the LCKD group ($P < 0.01$). The body weight was significantly reduced in all diabetic animals except in the LCKD group ($P < 0.01$). Histologic studies showed significant decrease in the islet size and number of β cells in all the diabetic groups.

Conclusion: This study indicates that LCKD has a significant beneficial effect in ameliorating the diabetic state and helping to stabilize hyperglycemia.

Keywords: Diabetes mellitus; Low-carbohydrate ketogenic diet; Streptozotocin; Biochemistry; Histology

Introduction

Diabetes mellitus (DM) is a serious universal health problem. The prevalence of this condition is rapidly increasing in the world. Similarly, in the Gulf region and especially in Kuwait, DM is spreading widely. Changes in lifestyle and dietary habits, in conjunction with genetic susceptibility, have resulted in a remarkable increase in the incidence and prevalence of diabetes in the world [1,2].

Type 1 diabetes, or insulin-dependent diabetes (IDDM), is caused by the autoimmune destruction of pancreatic β cells leading to insulin deficiency. Hence, the administration of insulin is essential for the metabolism and survival of these patients. Type 1 diabetes accounts for only 5–10% of all the diabetic cases [3]. Type 2 diabetes, on the other hand, is due to impaired insulin secretion and/or insulin resistance. This type of insulin-independent diabetes is much more widespread and accounts for almost 90–95% of the DM cases [4,5].

Recently several animal models have been used in the study of diabetes. Streptozotocin (STZ) is commonly used to alter pancreatic β-cell function leading to diabetes in experimental animals. STZ is a nitrosourea derivative [(2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose)], isolated from *Streptomyces achromogenes*, which selectively destroys pancreatic β cells [6]. It causes DNA methylation,

*Corresponding author. Tel.: 965-498-4875; fax: 965-498-3835.
E-mail address: tcmkwt@gmail.com (T. C. Mathew).

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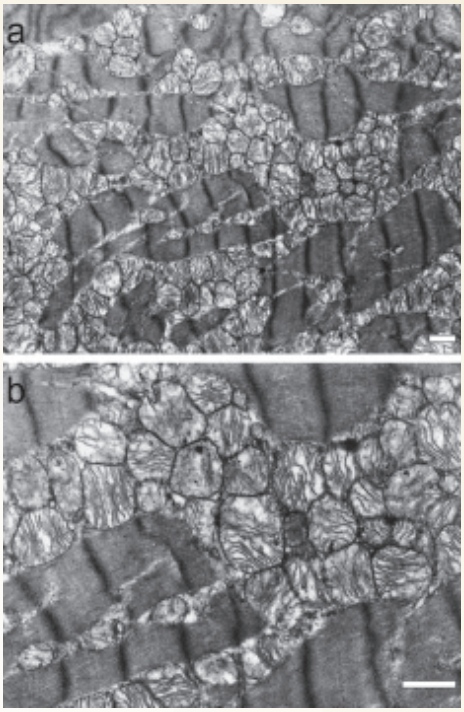

Micrograph showing the ultra-structure of the rat cardiac muscle following the administration of a low carbohydrate ketogenic diet (LCKD) at low (a) and high (b) magnification. There is an increase in the number of mitochondria in rats fed with a LCKD as compared to those belonging to the ND and HD groups. Bar = 1μm.

reduction in the number of mitochondria in the cardiac muscle of rats fed a high carbohydrate diet as compared to those fed normal rat chow. Furthermore, the cardiac muscle of rats in the LCKD group showed an increase in the number of mitochondria as compared to the ND and HCD groups. This is a clear indication of the metabolic efficiency of rats fed an LCKD as compared to the ND and HCD groups.

In order to understand further the mechanisms through which such an improvement in cardiac function works, we are planning further experimental work in order to explore the biochemical and functional changes at cellular level in rats subjected to different diets in order to elucidate the mechanisms involved. In conclusion, the reported results proved that a low carbohydrate ketogenic diet is cardio-protective functionally and the mechanism at the cellular level remains to be explored. Furthermore, we contend that dietary therapy with LCKD, in addition to other therapeutic measures may have a significant improvement on the clinical outcome of coronary artery disease patients.

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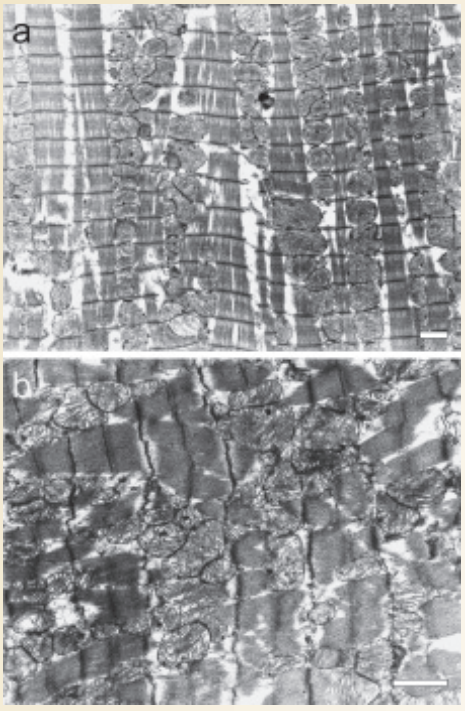

Fig. 3. – Micrograph showing the ultra-structure of the rat cardiac muscle at low (a) and high (b) magnification. Note the normal distribution of mitochondria in the cardiac muscle of adult rat that were fed normal rat chow. Bar = 1μm.

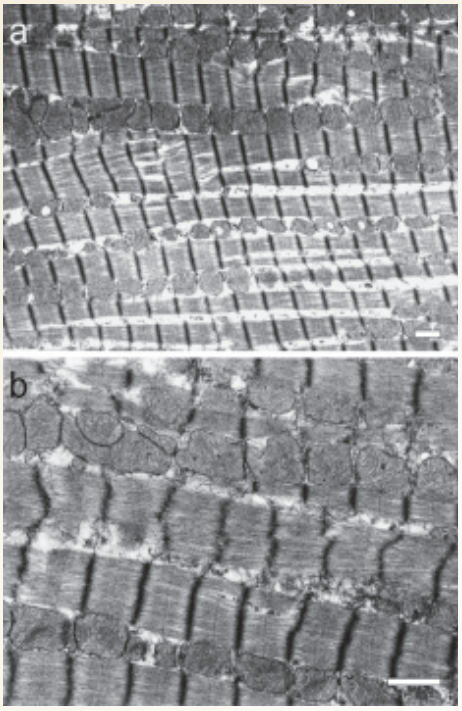

Fig. 4. – Micrograph showing the ultra-structure of the rat cardiac muscle following the administration of a high carbohydrate diet at low (a) and high (b) magnification. There is a decrease in the number of mitochondria in rats fed with a high carbohydrate diet (HCD) as compared to those fed with normal rat chow. Bar = 1μm.

systolic function of the hearts obtained from the low carbohydrate ketogenic diet group indicates better preservation of the myofilament functions. This beneficial effect may be due to the limitation of the activation of harmful proteases by the ketogenic diet with additive protection from improved post-ischaemic recovery in the coronary flow.

Rats on (LCKD) compared to the groups on (HC) and (NC) diets showed remarkable tolerance to ischaemia and the recovery of cardiac function after reperfusion was significantly faster. The improvement in cardiac function as indicated by the significant increase in the reperfusion recovery from induced ischaemia on the (Pmax) and (LVEDP) parameters are significantly improved compared to the control group and the group on a high carbohydrate diet. The areas under the curve for Pmax% and CF% were maximal for the LCKD group. Although the area under the curve for LVEDP% for the LCKD group was higher than normal, it was lower than that of the HC group. It should be noted that there was a rise in LVEDP% during the initial period of reperfusion, which could account for the increase in area under the curve as compared to the ND group. The overall results we are reporting, although limited, adds substantial experimental evidence that (LCKD) is advantageous.

It has been shown that LCKD increases the level and activity of the mitochondrial uncoupling protein (UCP) leading to an increase in proton conductance. The UCP-mediated protein conductance in turn diminishes the reactive oxygen species (ROS) production by reducing the electron transport through the mitochondrial respiratory chain. Furthermore, it has been shown that a ketogenic diet modifies the signal transduction mechanisms in neurons by altering the basal status of protein phosphorylation[21].

Further ultra-structural analysis of the cardiac muscles from the three different groups of animals further supports our view on the efficiency of LCKD in the faster recovery of cardiac function after reperfusion as compared to the groups on HC and NC diets in their tolerance to ischaemia. There was a significant

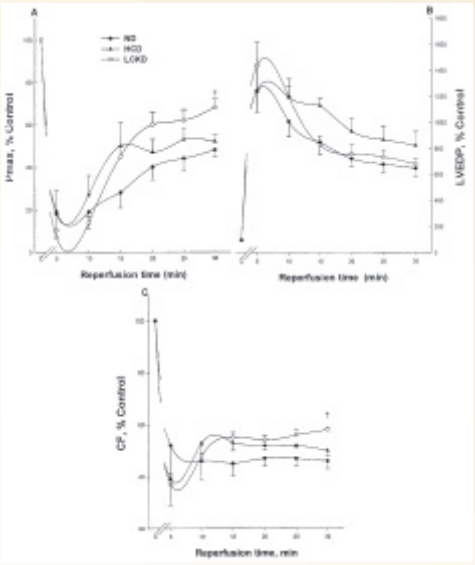

Fig. 2. – Time course of reperfusion recovery in (A) Pmax, (B) LVEDP and (C) CF after reperfusion in the normal diet (ND), high carbohydrate diet (HCD), and low carbohydrate ketogenic diet (LCKD) groups.

*Values significantly different from high carbohydrate diet (HCD) group, $P < 0.05$

LDL to a less atherogenic form[22]. On the other hand, several recent studies show a direct association of a diet with high glycaemic load and the development of cardiovascular disease, type II diabetes and certain forms of cancer[23-28]. A ketogenic diet, as compared to the traditional low fat diet has favourably improved glycaemic control, insulin sensitivity and dyslipidaemia of diabetes[22,29,30-36].

Additionally, animal experiments showed several advantages of (LCKD) in both normal and pathologically induced conditions[4,8,37]. The understandable concern about the long-term effects of LCKD on vital cardiac functions is mainly due to the scarcity of literature that concentrates on functional parameters in order to understand the mechanisms that operate at cellular level[38,39]. A recent review[40] explained the underlying cellular mechanisms of LCKD, however, many questions remain to be answered in this regard. The ketogenic diet is an adaptational process at cellular level leading to reliance on ketosis as an alternative source of energy through fatty acids oxidation instead of glucose.

Our result is in agreement with several reports that changes in body weight were not significant between the groups tested[41,42]. Therefore energy input and output, as explained in the results section, would eliminate body weight as an influencing factor in the outcome of the results of post-ischaemic recovery.

Myocardial ischaemic-reperfusion injury is well characterized[43] and is catalogued under those metabolic, functional and structural consequences of restoring coronary arterial flow in the ischaemically compromised heart. Both the length of the ischaemic insult and the speed and the pressure of reperfusion determine whether the cellular reperfusion damage can be reversible or irreversible. The reversible phase lasts for approximately 15 to 20 minutes during reperfusion and is followed by progressive irreversible injury that lasts for 30 to 90 minutes with extensive structural and functional damage. This irreversible phase results into depletion of the glycogen stores of the myocardium, mild mitochondrial swelling, increase in diastolic pressure, exaggerated release in enzymes and intracellular calcium, depletion of ATP and increase in myocardial infarct size[44,45]. Two major intracellular mechanisms have been reported to contribute to reperfusion injury: (i) the development of intracellular Ca^{2+} overload and (ii) oxidative stress due to increase in oxygen-derived free radicals[46-50]. The functional consequences for these mechanisms result in modified sensitivity of myofilaments to calcium through the activation of proteases that degrade myofilament proteins such as the troponin regulatory complex leading to a decrease in systolic pressure and an increase in end diastolic pressure[51,52]. From the results of the present study it can be visualized that the reperfusion functional recovery of the hearts obtained from normal diet (ND) and high carbohydrate diet (HCD) groups are in conformity with the classical description of the irreversible injury. However, significant preservation of the left ventricular

Table 3. – *Effect of experimental diets on the post-ischaemic recovery in coronary vascular dynamics.*

	Coronary flow			Coronary vascular resistance	
	Control	Reperfusion	%R	Control	Reperfusion
ND (n = 6)	14.5 ± 0.4	6.7 ± 0.6 *	46	3.2 ± 0.2	10.0 ± 1.3*
HCD (n = 5)	14.7 ± 0.5	7.3 ± 0.2 *	50	3.1 ± 0.2	10.3 ± 0.8*
LCKD (n = 5)	15.9 ± 0.6	9.1 ± 0.6 *#	58#	2.7 ± 0.1	8 ± 0.8*

The data was computed at 30 min reperfusion at 37°C and expressed as mean + SEM. % R, % recovery (ratio of reperfusion over control).* $P < 0.05$ when compared with respective control; # $P < 0.05$ when compared with HCD group.

Table 2. – *Effect of experimental diets on the post-ischaemic recovery in global contractility*

	Pmax (mm Hg)		%R	LVEDP (mm Hg)		%R	+dp/dt (mm Hg. sec^{-1})		-dp/dt (mm Hg. sec^{-1})	
	Control	Reperfusion		Control	Reperfusion		Control	Reperfusion	Control	Reperfusion
ND (n = 6)	113 ± 4	54 ± 4*	48	5.1 ± 0.1	33.3 ± 3.3*	649	3684 ± 103	1828 ± 105*	2920 ± 61	1372 ± 102*
HCD (n = 5)	113 ± 11	60 ± 8*	52	5.0 ± 0.1	42 ± 6*	825	4037 ± 209	1888 ± 146*	3131 ± 165	1404 ± 113*
LCKD (n = 5)	117 ± 14	74 ± 7*	64**	5.0 ± 0.2	35 ± 4*	687	3617 ± 220	2088 ± 150*	2798 ± 122	1617 ± 81*

The data was computed at 30 min reperfusion at 37°C and expressed as mean + SEM. Con, control; Rep, reperfusion; Pmax, left ventricular developed pressure; LVEDP, left ventricular end diastolic pressure; + dp/dt, positive derivative of pressure; -dp/dt, negative derivative of pressure; % R, % recovery (ratio of reperfusion over control)., $P < 0.05$ when compared with respective control; **, $P < 0.05$ when compared with HCD group.

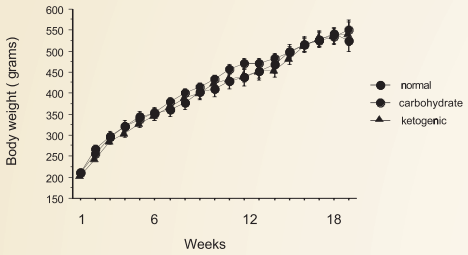

Fig. 1. – Time course of changes in the total body weight in the control and experimental groups.

Coronary vascular haemodynamics

Table 3 shows the mean (± SE) values for the reperfusion recovery of CF and CVR. Significant improvement in the reperfusion recovery of CF occurred only in the rats placed on a low carbohydrate ketogenic diet (LCKD) diet regime. Reperfusion recovery in the CF was 58 ± 2% in the LCKD group as compared to 47 ± 4% in the HCD group and the difference was significant ($P < 0.05$). However, no significant difference in the reperfusion recovery of CVR occurred and a 3-fold increase in CVR was observed in both experimental groups.

Figure 2 shows the time course for the 30 minutes reperfusion recovery of Pmax, LVEDP and CF. Initial recovery in Pmax was similar in all groups. However, after 10 minutes a faster recovery occurred in both the experimental groups. Whereas the recovery of Pmax in the HCD group plateaued at 15 min, the momentum for faster recovery in the LCKD group was maintained after 15 min and was significantly ($P < 0.05$) higher when compared with the HCD group. Reperfusion recovery in the CF essentially occurred in tandem with the recovery of Pmax in the LCKD group, and this recovery was significantly higher ($P < 0.05$) when compared with the HCD group. Areas under the curve for the 30 min reperfusion recovery of Pmax, LVEDP and CF in figure 2 were also calculated for the ND, HCD and LCKD group of animals. For Pmax the area under the curve for ND, HCD and LCKD were 1120, 1355 and 1360, respectively. For LVEDP, the area under the curve for ND was 24432.5, 29242.5 for HCD, and 26815 for LCKD. For CF the areas under the curve for ND, HCD and LCKD were 1550, 1620 and 1645, respectively.

Ultra-structural studies of the cardiac muscle

The cardiac muscles from the three different groups did not show any pathological changes at the ultra-structural level. The banding pattern of the myofibrils was similar in all three groups (figures 3-5). However, there was a significant reduction in the number of mitochondria in the cardiac muscle of rats fed a high carbohydrate diet (figures 4a, b) as compared to those fed with normal rat chow (figures 3a, b). Interestingly, the cardiac muscle of rats in the LCKD group (figures 5a, b) showed an increase in the number of mitochondria as compared to the ND and HCD groups. There was about 20% reduction in the number of mitochondria in the HCD group, while there was about 50% increase in the number of mitochondria in the LCKD group as compared to the control group.

Discussion

A low carbohydrate-ketogenic diet (LCKD) is currently appraised as a safe diet for the treatment of overweight and obesity in human subjects[10-12]. Furthermore, several reports[13-16] proved its efficiency as a treatment for type II diabetes and in reducing coronary heart disease risk factors.

In our previous studies, we have shown that long-term administration of a ketogenic diet, further to reducing body mass index ($P < 0.0001$), significantly decreased the level of triglycerides, LDL cholesterol and blood glucose, whereas there was an increase in the level of HDL cholesterol[11,12] and modification of

Table 1. – *Diet formulation and specification data for low carbohydrate ketogenic diet (LCKD) and high carbohydrate diet (HCD)*

		LCKD		HCD	
		Fresh	10% H20	Fresh	10% H20
Total	%	100.00	100.00	100	100
Moisture	%	10.04	10.00	12.54	10.00
Crude oil	%	12.65	12.66	3.46	3.56
Crude protein	%	57.50	57.53	16.29	16.76
Crude fibre	%	4.78	4.78	4.26	4.38
ASH	%	5.75	5.75	5.45	5.61
NFE	%	9.45	9.45	57.75	59.43
Pectin	%	0.91	0.91	1.48	1.52
Hemicellulose	%	1.96	1.96	10.86	11.18
Cellulose	%	5.55	5.55	4.19	4.31
Lignin	%	0.26	0.26	1.25	1.29
Starch	%	2.76	2.76	41.83	43.04
Sugar	%	1.48	1.48	3.68	3.79
Gross energy	MJ/kg	18.49	18.50	16.15	16.62
Digestible energy	MJ/kg	16.19	16.20	12.74	13.11
Metabolisable energy	MJ/kg	15.02	15.03	11.48	11.81
AT water fuel energy (AFE)					
AF energy	MJ/kg	15.95	15.96	13.68	14.08
AFE from oil	MJ/kg	30	30	10	10
AFE from protein	MJ/kg	60	60	20	20
AFE from carbohydrate	MJ/kg	10	10	70	70

followed. In brief, the method is as follows: the animals were anaesthetized with sodium pentobarbital (40 mg/kg) and perfused transcardially with a brief wash of 0.9% oxygenated saline, followed by 3% gluteraldehyde in Sorenson's buffer (0.1 M at pH 7.2). The hearts were dissected out and the cardiac tissues were post-fixed in the same fixative overnight. After dehydration in ethanol, the tissues were treated with propylene oxide for about 30 minutes. The tissues were then embedded in graded araldite mixture and blocks were prepared. Serial ultrathin sections were cut by a DuPont diamond knife. Some of the sections were stained with uranyl acetate followed by lead citrate. The ultrastructure of the stained sections was studied by Jeol 1200 transmission electron microscope. For histological studies and topgraphical identification 1 µm semithin sections stained with toluidene blue-borax solution were used.

Results

Body weight

Changes in the body weight were monitored over the 19 weeks of the dietary regime for all the groups of the study. The body weight showed a progressive increase from the mean base-line weight of 210.8 ± 7.3 g, 210.4 ± 3.2 g and 203.8 ± 14.6 g, to the mean weight of 525.0 ± 26.8 g, 551.8 ± 21.3 g and 542.5 ± 28.2 g for the rats of the ND, HCD and LCKD groups respectively (figure 1). There were no significant differences between the groups at any time period of measurement of body weight.

Left ventricular global contractile functions

Table 2 shows the mean (±SE) values for the Pmax and LVEDP for the ND and the experimental groups of rats. There was a significant increase in the reperfusion recovery of Pmax of the rats put on a low carbohydrate ketogenic diet regime (LCKD), while the rats put on a high carbohydrate diet (HCD) regime showed no significant change in the reperfusion recovery of Pmax when compared with their respective controls. Reperfusion recovery of Pmax of the low carbohydrate ketogenic diet group (LCKD) was 64.2 ± 7% and was significantly ($P < 0.05$) more pronounced when compared with the high carbohydrate diet (HCD) group. LVEDP increased 7-fold in the low carbohydrate ketogenic diet (LCKD) group as compared to 8 fold in the high carbohydrate diet (HCD) group but the difference was not significant.

as early as the beginning of the 20th century[1-3]. It is believed that the forced use of ketone bodies by the brain in a low carbohydrate scenario could be the plausible mechanism for the beneficial effect of ketogenic diets in epilepsy. It is also shown that LCKD is beneficial in the treatment of attention deficit/hyperactivity disorders[4], infantile spasms, bipolar illness[5-8], Alzheimer's disease[9] and brain tumour[10]. In contrast to the normal brain tissues that can derive energy from glucose and ketone bodies, tumour cells lack the metabolic versatility and are solely dependent on glucose for their energy requirements.

Several studies from our laboratory and other laboratories have convincingly shown the beneficial effects of a ketogenic diet in reducing weight among overweight and obese human subjects[10-18]. In addition, contrary to common belief, a ketogenic diet is found to be quite effective in reducing the risk of cardiovascular disease[10] and type II diabetes[19].

In rats, there were no histological changes in the muscle and brain after the administration of a ketogenic diet for 2 to 3 months[20], suggesting that long-term treatment with a ketogenic diet is not likely to develop lipid myopathy or neural inclusions[20,21]. Although various studies have shown the beneficial effects of LCKD on the health status of humans and animals, there are still some concerns about its cardiovascular risks. However, as far as we are aware of, studies dealing with the long-term effects of LCKD on cardiac muscle function are lacking. Therefore, the current study is focussed on animal models to understand the long-term effects of LCKD in preserving cardiac function from ischaemia/reperfusion-induced injury of isolated rat hearts as compared to rats fed on normal rat chow and high carbohydrate diets.

Materials and methods

Animals and experimental design

Eighteen male Wistar rats weighing 190-250 g were used in this study. The animals were fed on a standard laboratory diet (France Nutris Co. S.A.) and were provided water ad libitum. The animals were divided into control and experimental groups, consisting of 6 control animals (group I) and 12 experimental animals (groups II and III). Before the experiment all the rats consumed ad libitum a standard rodent diet. At the beginning of the experiment the animals were distributed randomly into three groups and assigned to normal (ND), LCKD and high carbohydrate diet (HCD) as follows:

group I: normal diet (ND),
group II: low carbohydrate ketogenic diet (LCKD; table 1),
group III: high carbohydrate diet (HCD; table 1).

The micronutrient composition of different diets is shown in tables 1-3. Food and water were given ad libitum throughout the experimental period. The amount of food and water intake by the different groups of animals was monitored.

Heart perfusion

Rats were anaesthetized with intraperitoneal sodium pentobarbital (60 mg/kg) and heparinized intravenously (1000 µg/kg) through the femoral vein. Hearts were immediately isolated and mounted on the perfusion apparatus and perfused retogradely with freshly prepared Kerbs-Hensleit solution (in mM: NaCl 117.9, KCI 5.59, $CaCl_2.2H_2O$ 2.4, $NaHCO_3$ 20, KH_2PO_4 1.19, $MgCl_2$ $6H_2O$ 1.2, Glucose 12.11; Osmolarity 300 mOsm, pH: 7.35). The perfusate was saturated with a mixture of 95% O_2 and 5% CO_2 at 37°C. An alcohol-filled latex balloon was introduced into the left ventricle and connected to a Statham pressure transducer (P23Db) and balloon volume was adjusted to give the baseline end diastolic pressure (LVEDP) of 5 mm Hg. Left ventricular developed pressure (Pmax) and its positive and negative derivatives (+dp/dt,-dp/dt) were monitored continuously. Coronary flow (CF) was measured by means of an electromagnetic flow probe positioned in the inflow tubing immediately above the aortic perfusion cannula. The perfusion pressure was kept constant at 50 mm Hg by means of a perfusion pressure control module of the perfusion assembly (Module ppcm type 671, HugoSachs Electronics, Germany). Coronary vascular resistance along with other haemodynamic data was computed every 10 seconds.

Hearts obtained from the control and the experimental groups were perfused for 30 minutes to obtain the baseline haemodynamic data. Thereafter they are subjected to 30 minutes of global ischaemia followed by 30 minutes of reperfusion (R) at 37°C. Myocardial temperature was monitored by a needle thermistor probe (Thermalert, Physitemp, USA), inserted at the apex of the heart of each perfused heart.

Post-ischaemic reperfusion left ventricular contractility and haemodynamics were recorded and compared. Reperfusion values were compared with their respective baseline controls using a two tailed paired t-test. Comparison between different experimental groups was done by a general factorial analysis of variance. Comparison of the time-course of changes in reperfusion recovery of Pmax, LVEDP and CF was done by a two tailed t-test for each time period. Computerized statistical analysis was done with SPSS for window (version 6.0.1. SPSS Inc., Evanston, IL, USA).

Ultra-structural studies of the cardiac muscle

Three animals from each group (ND, LCKD and HCD) were used for this study. For transmission electron microscopic studies, the routine procedure was

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البحث السادس

ORIGINAL ARTICLE

Low carbohydrate ketogenic diet enhances cardiac tolerance to global ischaemia

Naji AL-ZAID[1], Hussein DASHTI[2], Thazhumpal MATHEW[3], Jaspir JUGGI[1]

[1]Departments of Physiology, [2]Surgery, [3]Faculty of Medicine and Faculty of Allied Health Sciences, Kuwait University, Kuwait.

Summary — The cardio-protective effects of a low carbohydrate ketogenic diet following global ischaemic injury as compared to rats fed a normal and high carbohydrate diet for a period of 19 weeks, were investigated. The reperfusion recovery of coronary flow was highly significant in the low carbohydrate ketogenic diet group. Although the initial reperfusion recovery of the pressure developed in the left ventricle, Pmax was similar in all groups, after 15 minutes, the momentum for faster recovery was maintained in the low carbohydrate ketogenic diet group. Ultrastructural observations of the cardiac muscles have shown that there was a decrease in the number of mitochondria in rats fed a high carbohydrate diet and an increase in the number of mitochondria in those fed a low carbohydrate ketogenic diet as compared to the normal diet group. This study demonstrates that a low carbohydrate ketogenic diet is cardio-protective functionally.

Introduction — Ischaemia and reperfusion lead to cell death. These pathways are regulated and hence are subjected to therapeutic intervention. Previously, we have shown that a low carbohydrate ketogenic diet (LCKD) reduces the risk factors for heart disease in obese patients. This study is aimed at understanding the cardio-protective effects of LCKD following global ischaemic injury in rats.

Materials and methods — Rats weighing 190-250 g were divided into normal diet (ND), LCKD and high carbohydrate diet (HCD) groups consisting of six animals in each group. Specific diets were given to each group for a period of 19 weeks. Changes in body weight, ultrastructure of the cardiac muscles and the cardio-protective effects of the LCKD group as compared to the ND and HCD groups were investigated in rats following global ischaemic injury.

Results — Electron microscopic studies have shown that there was a decrease in the number of mitochondria in rats fed a high carbohydrate diet and an increase in the number of mitochondria in those fed a low carbohydrate ketogenic diet as compared to the normal diet group. Rats on LCKD had a remarkable tolerance to ischaemia and a faster recovery of cardiac function following reperfusion. The initial reperfusion recovery of the pressure developed in the left ventricle, Pmax was similar in all groups. However, after 15 minutes, the momentum for faster recovery was significantly maintained in the LCKD group ($P < 0.05$). The reperfusion recovery of coronary flow was highly significant ($P < 0.05$) in the LCKD regime. The increase in left ventricle end diastolic pressure, coronary vascular resistance and the changes in body weight were not significant between the experimental groups.

Discussion and conclusion — This is a unique study showing ultrastructural variation in cardiac muscle in relation to cardio-protective function in rats fed a low carbohydrate ketogenic diet. This study suggests that the LCKD is cardio-protective functionally. The underlying mechanism of the cardio-protective effect of an LCKD needs to be elucidated.

Keywords: *obesity – low carbohydrate ketogenic diet – ischaemia – reperfusion – cardiac tolerance – vascular haemodynamics.*

Address for correspondence: Prof. Hussein Dashti, M.D., Department of Surgery, Faculty of Medicine, Kuwait University Health Sciences Center, P.O Box 24923, 13110 Safat, Kuwait. E-mail: Dashti@hsc.edu.kw

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Introduction

A low carbohydrate ketogenic diet (LCKD), a revolutionary form of diet therapy for obesity, was introduced as an effective treatment for intractable epilepsy

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CONCLUSION

The data presented from the various studies conducted at the Faculty of Medicine, Kuwait University, in a population comprising of Kuwaiti and non-Kuwaiti subjects and the results of several investigators mentioned in this review show that a ketogenic diet (consisting of 30 gms carbohydrate, 1 gm/kg body weight protein, 20% polysaturated, 80% polyunsaturated and monounsaturated fat) induces a miraculous weight loss in normal obese subjects as well as obese subjects with diabetes and hyperlipidemia. In addition to weight loss, there was a significant decrease in the level of triglycerols, total cholesterol, LDL-cholesterol and glucose whereas there was an increase in the level of HDL in these patients. Also, recent studies have shown that LCKD may actually be cardio-protective. All these studies clearly indicate that it is a safe to administer ketogenic diet for a diet for a relatively long period.

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Table 7: Statistical significance between week 1 and week 56 observation of various parameters studied in group I (high cholesterol) and group II (normal cholesterol) subjects[66].

	Total (n = 66)	Group I (n = 35) High cholesterol	Group II (N = 31) Normal cholesterol)
Weight (kg)	< 0.0001	< 0.0001	< 0.0001
BMI (kg/m^2)	< 0.0001	< 0.0001	< 0.0001
Total chol (mmol/l)	< 0.0001	<0.0001	0.0170
HDL (mmol/l)	< 0.0001	< 0.0001	< 0.0001
LDL (mmol/l)	< 0.0001	< 0.0001	< 0.0001
TG (mmol/l)	< 0.0001	< 0.0001	0.0002
Glucose (mmol/l)	< 0.0001	< 0.0001	0.0034

is the most important factor that influences the glycemic level. LCKD appear to improve glycemic control and lessen the need for exogenous insulin and hypoglycemic medication[67,72]. Furthermore, LCKD significantly improved the insulin sensitivity by up to 75%[54,73]. In a recent study on experimental rats from our laboratory, we have demonstrated that LCKD ameliorated the diabetic state and helped to stabilize hyperglycemia. In addition to its therapeutic effect, LCKD had a significant protective role against the diabetogenic action of streptozotocin (STZ) [74]. STZ is selectively cytotoxic to the ß-cells of pancreatic islets. Therefore it is commonly used to induce diabetes in experimental animals[74].

Osteoporosis

A link between low fat diet and osteoporosis has been suggested. Very-low-fat diets are considered to be low in calcium content. Women on low-fat diets excrete most of the calcium they consume. Therefore, they are more prone to osteoporosis. On the other hand recent studies indicate that a high fat diet can rectify this situation[75].

Cancer

The relation between high fat diet and cancer is close to reality now. It has been found that altered energy metabolism and substrate requirements of tumor cells can provide a target for cancer therapy. Two major metabolic alterations found in cancer cells are the increase in glucose consumption and aerobic glycolysis, the conversion of glucose to lactic acid *via* the reduction of pyruvate even in the presence of oxygen. In addition, there are defects in ketone body metabolism[71,76]. These metabolic changes in cancer cells may provide a rationale for therapeutic strategies that inhibit tumor growth by LCKD. It has been shown that cancers, specifically brain tumors grow minimally on a LCKD[77]. These studies suggest that treatment with LCKD is a safe and effective alternative therapeutic option for malignant brain cancer. In addition, ketone bodies function as anti-inflammatory agents through the reduction of reactive oxygen species and increase of glutathione peroxidase activity[78].

SIDE EFFECTS OF KETOGENIC DIET

It is noticed that some individuals on ketogenic diet may experience a bad breath. However, vast majority of individuals do not develop medical problems. As in the case of any form of diet with restricted caloric intake, ketogenic diet is also deficient in minerals and water-soluble vitamins [79]. In order to overcome the side effect, subjects on ketogenic diet are given multi vitamin and mineral supplements daily to avoid such deficiencies.

Another criticism of ketogenic diet is the reduction of fruits, vegetables and whole grains, which are considerd to be healthy foods. However, it should be noted that LCKD can include a wide range of healthy vegetable as mentioned in Table 2. It has been suggested that chances of having increased formation of kidney stones could be another side effects of LCKD. Factors that could enhance the stones formation could be the restricted fluid intake and increased production and the decreased excretion uric acid. Also, similar to suppression of food intake, ketone bodies are involved in the suppression of thirst leading to the reduction in the fluid intake. Thus hyperuricemia gives rise to urate stone formation. It is suggested that with 5% carbohydrates composition in the diet this situation can be prevented[80]. It should be noted that, in our studies we have observed a decrease in serum level of urea (Tables 3, 4).

Constipation is also a noted side effect of LCKD. This could be due to the decreased fiber content and as mentioned above the suppression of thirst by ketones leading to dehydration. Also, with increased absorption / digestion of foods, there is a decrease in the stool volume. This situation can be easily avoided by increasing the fiber content by taking in vegetables in the diet, increasing fluid intake and using sugar-free laxatives[34,81]. Apart from these, the data presented in this review from our laboratory and from the studies of various investigators show that chronic ketosis without caloric restriction poses no danger to maintaining a healthy body.

Table 5: Baseline values of different physical and biochemical parameters monitored in persons (high cholesterol / normal cholesterol) subjected to low carbohydrate diet (ketogenic diet) [66]

	Total	Group I (n=35) (High cholesterol)	Group II (n=31) (Normal cholesterol)	p-value
Age (years)	42.9+10.8	45.5+9.2	39.9+11.8	0.0731
Weight (kg)	106.9+18.3	112.3+19.3	100.7+15.3	0.0168
BMI (kg/m^2)	39.1+6.1	40.1+6.1	38.0+6.1	0.1385
Tot.chol. (mmol/l)	6.1+1.4	7.0+0.9	5.0+0.8	<0.0001
HDL (mmol/l)	1.1+0.3	1.1+0.3	1.2+0.3	0.0076
LDL (mmol/l)	4.6+ 1.2	5.4+0.8	3.6+0.7	<0.0001
TG (mmol/l)	3.2+2.3	4.3+2.6	2.0+1.1	<0.0001
Glucose (mmol/l)	7.7+3.4	9.4+3.7	5.7+1.5	<0.0001

HDL = high density lipoprotein; LDL = low density lipoprotein; TG =Triglyceride ; Tot.Chol.= Total cholesterol
Data is expressed as mean + standard deviation

with high cholesterol level and obese diabetic subjects were treated with LCKD for longer period, suggesting that it is safe to use ketogenic diet in both diabetic subjects (Table 3, 4) and in subjects with high cholesterol level (Table 5, 6). Further studies revealed that despite the increase of cholesterol intake with ketogenic diet, there is no significant increase in the total cholesterol or LDL[53,64-67]. This may be due to the low insulin level which will activate HMG CoA lyase, the enzyme responsible for ketone formation and inhibit HMG CoA reductase, the enzyme responsible for cholesterol formation[68]. In a recent study from our laboratory on experimental rats, we have convincingly shown that LCKD enhances cardiac tolerance to global ischemia as compared to rats fed on a high carbohydrate diet [69]. In addition, ultra structural studies have shown that there was a decrease in the number of mitochondria in rats fed a high carbohydrate diet and an increase in the number of mitochondria in those fed a LCKD as compared to the normal diet group, confirming the physiological observations on cardio-protective function of LCKD[69]. It should be noted that pre-historic diets were high in dietary protein and fat. However, these pre-historic societies were relatively free of several cardiovascular diseases that exist today in our society[35].

Diabetes mellitus and insulin resistance

In the pre-insulin era LCKD has been used for diabetes treatment instead of medications[70]. The results from our laboratory show that LCKD has significant beneficial effects in obese diabetic subjects following its long-term administration (Table 3, 4). The blood glucose level decreased significantly from the start until the 56th week. A similar situation was found when obese subjects with high cholesterol level were treated with LCKD for longer period, suggesting that it is safe to use ketogenic diet in both obese diabetic subjects and subjects with high cholesterol level (Table 5, 6). Furthermore, LCKD may be effective for improving glycemia and reducing medications in patients with type II diabetes. Insulin resistance is a characteristic feature of Type 2 diabetes[71]. Insulin resistance is defined as the inability of insulin to produce its usual response at concentrations that are effective in normal individuals. As mentioned earlier, the content of carbohydrate in the diet

Table 6: Percentage changes in the various parameters observed at week 56 in persons (high cholesterol / normal cholesterol) subjected to ketogenic diet[66]

	Total (n = 66)	Group I (n = 35) High cholesterol	Group II (n=31) Normal cholesterol	p-value
Weight (kg)	-25.9+6.3	-25.8+6.7	-26.0+5.8	0.9065
Total chol (mmol/l)	-19.3+17.0	-29.2+9.4	-6.2+16.2	0.0005
HDL (mmol/l)	52.3+43.8	63.7+52.7	37.1+20.6	0.1778
LDL (mmol/l)	-28.2+20.1	-33.5+19.5	-21.3+19.1	0.1331
TG (mmol/l)	-59.0+32.1	-69.8+32.6	-44.7+25.7	0.0537
Glucose (mmol/l)	-31.0+25.0	-44.0+22.6	-12.8+15.1	0.0004

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride ; Tot.chol.= Total cholesterol
Data is expressed as mean + standard deviation. Statistical significance between Group I and Group II are given.

loss of energy in the form of heat[46] and in the form of ketones in urine, sweat, and feces.

In addition to the weight loss observed, very-low-carbohydrate ketogenic diets alter the metabolic rate by preserving more lean body mass[47]. Following the administration of ketogenic diet there is a preferential loss of fat mass and preservation of more lean body mass[47-49]. As mentioned earlier, ketone bodies especially BHB, has an effect on appetite suppression[50]. In addition, the high fat content in LCKD delays the digestion providing a sense of fullness[51]. Above all, the utilization of fat as body fuel, promote fat loss and therefore weight loss[52]. In addition to studies from our laboratory, several other studies have shown that low carbohydrate diets compared to low fat diets have a significant long term effect on the reduction of body weight[53-55].

OTHER BENEFICIAL EFFECTS OF KETOGENIC DIET

Although, the main focus of this review is on the beneficial effects of ketogenic diet on obesity, we know that this review will not be complete, if some of the other beneficial effects of ketogenic diets are not mentioned. Therefore, we give here below, some well known beneficial effects of ketogenic diet on neuronal and cardiac efficiency and its therapeutic role in diabetes, heart diseases, cancer *etc*.

Brain function

In humans, ketone bodies are the only additional brain energy source after glucose[56,57]. Hepatic generation of ketone bodies during fasting is a protective mechanism that spares the destruction of muscle from glucose synthesis. Historically, it is known that ketogenic diet is quite effective in antiepileptic treatments. However, how this diet works is still unclear? Several mechanisms that contribute to the anticonvulsant role of LCKD have been suggested. It is found that ketogenic diet increases the synthesis of the inhibitory neurotransmitter XY-aminobutryric acid (GABA) in the brain, which may be involved in the suppression of the seizure activity[58]. Furthermore, LCKD increases the level of polyunsaturated fatty acids (PUFAs), which functions as modulators of neuronal membrane excitability by inhibiting the sodium and calcium ion channels[59]. It is suggested that free radicals contribute to the development and progression of epilepsy. Thus, the anticonvulsant role of ketogenic diet could also be through the antioxidant mechanisms activated by fatty acids and ketones[60]. It has also been found that a ketogenic diet affects signal transduction in neurons by inducing changes in the basal status of protein phosphorylation[61]. Furthermore, ketogenic diet has beneficial influence on the brain energy metabolism[62].This is quite significant, as cerebral hypometabolism is a characteristic feature of those who suffer from depression or mania[62]. Interestingly, it is shown that a ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease[63].

Cardiovascular Diseases

The common notion is that a ketogenic diet will cause high cholesterol, TAG, and cardiovascular disease because of the high fat it contains. In our previous studies and recent studies using ketogenic diet it is shown that LCKD decreased the level of triglycerol and LDL cholesterol and increased the level of HDL cholesterol[53,64-67]. Furthermore, administering a ketogenic diet for a relatively longer period of time did not show any significant side effects in the patients. A similar situation was found when obese subjects

Table 3: Statistical significance between week 1 and week 56 observation of various parameters studied in normal subjects[67].

	Normal subjects (n=33)		
	Week 1	Week 56	p-Value
Weight (kg)	108.081+21.245	83.536+18.030	<0.0001
Total chol (mmol/l)	6.755+1.086	4.878+0.533	<0.0001
HDL (mmol/l)	1.033+0.264	1.586+0.211	<0.0001
LDL (mmol/l)	5.160+0.892	3.379+0.608	<0.0001
TG (mmol/l)	4.681+2.468	1.006+0.205	<0.0001
Glucose (mmol/l)	10.481+3.026	4.874+0.556	<0.0001
Urea (μmol/l)	5.778+0.905	4.972+1.050	<0.0111

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride
Data is expressed as mean + standard deviation.

Table 4: Statistical significance between week 1 and week 56 observation of various parameters studied in diabetic subjects[67].

	(n = 31; Diabetic subjects)		
	Week 1	Week 56	p-Value
Weight (kg)	105.273+15.377	74.923+11.384	<0.0001
Total chol (mmol/l)	5.479+1.293	4.650+0.495	0.0020
HDL (mmol/l)	1.237+0.270	1.621+0.177	<0.0001
LDL (mmol/l)	4.030+1.148	2.807+0.496	<0.0001
TG (mmol/l)	1.827+0.981	0.861+0.179	0.0001
Glucose (mmol/l)	5.127+0.440	4.726+0.529	0.0069
Urea (μmol/l)	5.563+1.299	4.419+0.743	<0.0001

HDL=high density lipoprotein; LDL=low density lipoprotein; TG=Triglyceride
Data is expressed as mean + standard deviation.

But these two conditions are quite different and virtually opposite. Diabetic ketoacidosis has high blood sugar while ketosis has a high blood level of ketone bodies. Is ketosis safe? If ketosis was bad for health, why does nature switch on to a situation similar to that of administering a ketogenic diet? Well, everyone approaches ketogenesis during the sleep portion of the diurnal cycle. Above all, who can ignore the fact that mother's milk, which has a high fat content, is the best natural food formula taken in during human development? It is also interesting to note that no species could have survived millions of years, if its members could not tolerate occasional brief periods of natural starvation, which results in ketosis.

WHAT ARE KETONE BODIES?

Ketone bodies result from the partial oxidation of free fatty acids and are synthesized only in the mitochondria of liver cells. There are three types of ketone bodies. They are: acetoacetate (AcAc), ß-hydroxybutyrate (BHB), and acetone. Ketone bodies are always being produced under normal dietary conditions but in amounts that are too small to cause any metabolic effects[37]. Triacylglycerol (TAG) stored in fat tissue breaks down into glycerol and three fatty acid molecules. This process is lipolysis and is regulated by hormones like glucagon, epinephrine *etc*. These hormones activate the hormone-sensitive lipase (HSL) that hydrolyzes fatty acid from carbon atom 1 and / or 3 of TAG. The remaining fatty acids are removed by other lipases that are specific for diacylglycerol or monoacylglycerol[38].

Fatty acids are classified into short-medium chain fatty acids consisting of 12 carbons or less and long chain fatty acids. Medium chain fatty acids are found in the maternal milk and in medium chain fatty acid oils. The free fatty acids that diffuse from adipose cells either bind with albumin in the blood or remain as free fatty acids. The albumin bound fatty acids are transported to other tissue to be oxidized and the unbound free fatty acids present in the blood reach the liver[38, 39]. The medium chain fatty acids enter the liver without any transporter whereas the long chain fatty acids, the major precursor for ketone bodies, need a special transporter called carinitine to enter the mitochondrial matrix and become oxidized[40].

The medium chain fatty acids become activated to fatty acyl CoA and undergo ß-oxidation to form fatty acetyl CoA whereas the long chain fatty acids become activated into fatty acyl CoA in the liver cytosol. The carinitine acyltransferase system moves the acyl CoA to the mitochondrial matrix where they undergo ß-oxidation to form acetyl CoA[40]. When there is an excess of acetyl CoA, more than that is required for providing energy through Kerb's cycle, the liver converts the extra acetyl CoA into ketone bodies[41,42].

The formation of ketone bodies occurs as follows. Two molecules of acetyl CoA are condensed to form a molecule of acetoacetyl CoA. Then a third molecule of acetyl CoA is added to acetoacetyl CoA to form 3-hydroxy-3-methylglutaryl CoA (HMG CoA). Formation of HMG CoA is catalyzed by the hepatic enzyme, HMG CoA synthase. HMG CoA is then cleaved into acetyl CoA and acetoacetate by the action of another enzyme, HMG CoA lyase. Acetoacetate is either reduced to ß-hydroxybutyrate (BHB) through the action of BHB dehydrogenase or undergoes spontaneous decarboxylation to acetone which is excreted in the breath and urine[41,42].

Ketone bodies are used as an energy source in the body including the brain. BHB is converted to acetoacetate by the reversal reaction of BHB dehydrogenase, producing nicotinamide adenine dinucleotide phosphate (NADH). The acetoacetate, in turn, will bind to coenzyme A (CoA) provided from succinyl CoA molecules through thiophorase reaction producing acetoacetyl CoA. The acetyl CoA is further converted into two molecules of acetyl CoA, which will enter the Kreb cycle for production of energy[42].

EFFECT OF KETOGENIC DIET IN PREVENTING OBESITY

Recent studies from our laboratory have shown that the ketogenic diet is a natural therapy for obesity even in diabetic subjects. The weight and body mass index of the patients decreased significantly ($p < 0.0001$) from week 1 to 56 (Table 3). A similar significant ($p < 0.0001$) weight loss was observed in diabetic subjects who were on a LCKD diet (Table 4).

Several possible mechanisms on the role of very-low carbohydrate diet in reducing body weight have been suggested[43]. It is thought that major part of the weight loss following the administration of ketogenic diet can be attributed to the loss of water. Each 1 g of glycogen is stored in 3 gms of water. This means that the initial weight loss could be due to glycogen depletion and water excretion in urine. The weight lost in this manner will be gained immediately after stopping the ketogenic diet. Glycogen stores replenishes again with retention of a large amount of water as mentioned above[44,45]. Ketones have a diuretic effect and hence lead to an even greater water loss[44]. Furthermore, there is a decrease in metabolic efficiency resulting in greater

Table 2: Recommended and restricted food in ketogenic diet[66]

Recommended Food			Fully Restricted Food	
Proteins	**Vegetables/Fruits**	**Oil**	**Carbohydrates**	**Fruits/drinks**
Fish: Tuna,Sardine Prawns, Shrimps. Lobster **Meat:** Kababs, Sausages, Minced **Poultry:** Chicken, Eggs **Cheese:** Full fat cheese	Spinach, Watercress, Eggplant, Parsley, Mulberry, Coriander, Mint, Artichoke, Okra, Cabbage, Mushroom, Avocado, Leek, Carrot, Radish, Celery, Cauliflower, Green pepper, Lettuce, Cucumber, Tomato, 10-15 olives/day, Lemon, Strawberry -6/day, Avocado, Berries-10/day	Olive oil (5 tablespoon, added to the salad) Flax seed oil	Flour, Potato, Macaroni Spaghetti, Noodles, Bread, Rice, Sugar, Sweets, Honey, Cakes	All fruit juices All soft drinks

improve the lipid disorders that are characteristic of atherogenic dyslipidemia[32]. Furthermore, high insulin levels lead to increased risk of breast cancer and polycystic ovarian syndrome[6,19,33]. In addition, other evidence indicates that consumption of a high–glycemic-index diet is associated with a higher risk of diabetes.

Excess sugar in the bloodstream also leads to the production of free radicals. Free radicals increase significantly one hour after sugar consumption and more than double after two hours. It has been proven that disrupting the oxidant-antioxidant status of the cell will lead to various diseases of the body[33]. Furthermore, increased sugar decreases the blood levels of vitamin E, which leads to a decrease in the natural ability of the body to fight against free radical damage.

Carbohydrates increase levels of triglycerol, total cholesterol, and low density lipoprotein (LDL) and decreases HDL cholesterol. High ratio of triglycerol to HDL has a 16-fold greater incidence of coronary events than those with the low ratio[10,19,22,32]. In several studies, insulin, insulin-like growth factors and carbohydrates were identified as risk factors for cancer. It is quite reasonable to believe that sugar contributes to the growth and metastasis of cancer since cancer cells utilize sugar as their energy source. In other studies it was found that sugar is a causative factor in kidney disease, liver disease and shortened life span. Although there is cumulative scientific evidence to show that high carbohydrate diets can cause more harm than previously thought, we are still unwilling to accept this fact.

Since the 1980's calories from fat intake dropped from 34 to 8%. However, no change in the trend of obesity has been noticed. Interestingly, even after all this; the negative image of fat is still in our mind. In fact, contrary to the common belief, high fat diet has certain therapeutic values. Since 1921, high fat diet was used as an effective alternative therapy to control intractable seizures[34]. In some cases, high fat diet was found to be far better than modern anticonvulsants. The common argument against the consumption of high-fat diet is that it causes obesity. However, recent studies show that the high fat diet can cure obesity. Since obesity results from genetic and environmental influences, an individualized approach probably is the best solution for tackling the obesity problems. Therefore, a low-carbohydrate diet combined with an exercise program, in our experience, can help selected patients to safely achieve weight loss and overcome several obesity associated diseases. As mentioned earlier, since lower insulin levels and less hunger are the physiologic effects of consuming foods with low–glycemic-index, persons who take in low-carbohydrate diets could successfully lose their weight. Furthermore, there is an increased calorie use *via* ketogenesis. Therefore, LCKD is a reasonable alternative for body weight loss for persons who are willing to adhere to this diet. Table 2 gives a brief list of recommended and restricted food in ketogenic diet.

Low carbohydrate ketogenic diets

LCKD is not new to our society. Even early man's prehistoric diets may have been low carbohydrate ketogenic diets[35]. Prior to its use as a diet for obesity, LCKD have been used in the treatment of diabetes[36] and pediatric epilepsy[34]. Also, studies on the therapeutic role of LCKD in obesity are not new at all. Since 1955, scientists were experimenting on the concept that fat can be eaten *ad libitum* and still induce weight loss in obese subjects. A high-fat diet changes the body's metabolism to a new direction. Incomplete oxidation of fatty acids by the liver, results in the accumulation of ketone bodies in the body. The condition in which ketone bodies are formed in excess of the body's ability to metabolize them is called ketosis. Since high-fat diet causes ketosis, they are generally called as ketogenic diets. Ketosis has a significant influence on suppressing hunger. Thus, a ketogenic diet is a good regulator of the body's calorie intake and it is the body's natural adaptation to starvation. However, this mild ketosis has been always confused by the general public with the dangerous ketoacidosis which is associated with untreated type I diabetes. Ketosis is often confused with diabetic ketoacidosis.

Table 1: Obesity associated risks

Mild risk	Moderate risk	Severe risk
• Low back pain • Impaired fertility • Increased risk during anesthesia • fetal defects due to Maternal obesity • Cancer	• Coronary heart disease • Hyperuricaemia • Gout • Osteoarthritis • Complications of pregnancy	• Diabetes • Dyslipidaemia • Hypertension • Gall bladder disease • Sleep apnoea • Breathlessness

achieving a sustainable health service. Along with the appropriate measures taken to prevent obesity, priority should be given to the treatment of obesity related diseases. The health consequences of obesity can be categorized into mild, moderate and severe types depending on the risk involved (Table 1).

CONTRIBUTING FACTORS TOWARDS OVERWEIGHT AND OBESITY

Obesity results from the interplay between genes and environment. Both genes and behavior may be needed for a person to become overweight. Other factors that regulate body weight are the diet preferences and the number of calories consumed. One of the genetic components of obesity is insulin resistance which is the probable common pathway for metabolic syndrome. It has been shown that diet choices and physical activity are the major contributing factors towards overweight and obesity. Caloric intake must be equal to the caloric expenditure to maintain a healthy body weight. Calorie, the unit of energy is defined as the amount of heat needed to raise the temperature of one gram of water by one degree Celsius at sea level. By eating roughly the same number of calories that the body requires, the body weight can be maintained in a stable condition. Obviously, weight gain occurs when more calories are taken than the body requires. The extra calories taken in are stored as fat within the body. However, this fact is true only when eating a lot of carbohydrate along with fat. On a diet with controlled amounts of carbohydrate, the body will switch from using glucose to fat for producing energy. This means that a person on low carbohydrate ketogenic diet (LCKD) can take in as much calories and still loose weight. In other words, a person while consuming 3,000 calories on LCKD will loose weight whereas taking in the same calories on a low-fat high carbohydrate diet will gain weight. So the assumption that the only way to lose weight is to strictly control the intake of calories needs to rewritten based on the type of diet. Furthermore, while on LCKD diet the appetite is usually diminished and a person will eat only fewer calories. Hence persons on LCKD will have to burn more fat for producing energy, which will lead to more weight loss.

Another factor that needs to be mentioned is the outcome of certain diet programs that restrict calorie intake. In such circumstances where diets with restricted calories are taken, so as to conserve energy, the overall metabolism in the body shifts into a slow survival mode. But after certain period, when it becomes inevitable for the person on the low calorie diet to go back to a higher-calorie diet, the body metabolism will still remain in its slow survival mode of burning calories slowly. Hence it becomes quite difficult to continue or maintain weight loss in such situations.

OBESITY IN RELATION TO DIET PREFERENCES

Since obesity is the accumulation of excess of body fat, excessive fat intake has been discouraged. Less fat and exercise had become the slogan against obesity to be fit physically and maintain a healthy body. Well, for generations people have tried this recipe of low fat diet, yet they still get obese. Therefore, what we blindly believe about high carbohydrate diet could be completely baseless.

Various researchers have pointed out the bad effects of a high carbohydrate diet. It is the root cause of various chronic diseases. Several studies[7-18] have shown that a diet with a high glycemic load is independently associated with accelerated aging, development of cardiovascular diseases, type II diabetes and certain forms of cancer[7-9].

The glycemic index is a rating system for foods based on their ability to raise the level of blood glucose within two hours of their consumption[19]. When foods of higher glycemic index are eaten there is a rapid release of glucose into the bloodstream. The glycemic index of pure glucose or white bread is arbitrarily scored as 100[20]. Foods with high glycemic index induce a rapid release of insulin[19]. Thus eating foods with a high glycemic index lead to higher levels of circulating insulin. This rapid surge in insulin release can cause a relative hypoglycemic period within the postprandial period. The reactive hypoglycemia thus developed with foods of lower fat and higher carbohydrate content stimulates the appetite and thus leads to obesity[21]. The hyperinsulinemia developed following the consumption of foods with high glycemic index has been implicated in creating atherosclerotic plaques, that can lead to heart disease[22]. Insulin increases salt and water retention, a mediator of high blood pressure and correlates with high levels of triglycerol and low levels of high density lipoprotein (HDL) cholesterol. Now it is evident that high carbohydrate diets increase fasting plasma triglycerol concentrations[23-27] and decrease HDL cholesterol concentrations[28-30]. These changes are associated with enhanced atherogenesis[31]. However, it is found that short-term ketogenic diets

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Review Article

Prevention of Obesity Using Low Carbohydrate Ketogenic Diet

Hussein M Dashti[1,2], Thazhumpal C Mathew[2,3]
[1,2]Departments of Surgery and Anatomy, Faculty of Medicine
[3]Department of MLS, Faculty of Allied Health Science, Kuwait University, Kuwait

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ABSTRACT

This review focuses on the effect of low carbohydrate ketogenic diet on obese subjects presenting with various metabolic syndromes. Here, we provide data from our laboratory and from various other investigators on the therapeutic effectiveness of ketogenic diet on obese subjects. In this review we provide the rationale behind using ketogenic diet as a treatment of obesity and its beneficial role in neurodegenerative / neurological disorders, diabetes, hyperlipidemia, coronary diseases, cancer *etc.* Administering ketogenic diet for a relatively longer period did not produce any significant side effect. Therefore, based on the data presented in this review, it is recommended that it is safe to use ketogenic diet for a longer period of time for obesity and associated disorders.

KEY WORDS: coronary diseases, diabetes, hyperlipidemia, low carbohydrate ketogenic diet, obesity

INTRODUCTION

Although, historically obesity has been considered as a sign of a prosperous and wealthy society, today obesity has become a major health problem in both developed and developing countries. Obesity has been described as a disease entity since 1700s. Currently obesity levels are increasing at a remarkable level all over the world. Data from a recent survey by the US Center for Disease Control indicates that 66% of the US population are overweight, with 32.3% having a body mass index (BMI) of more than 30 kg/m^2[1]. It is estimated that about 300,000 people die each year from obesity related diseases[1]. A similar trend is observed in Kuwait and other Middle East countries[2].

CLASSIFICATION OF OBESITY

Obesity has been defined by body mass index (kg/m^2) and waist circumference. According to the current classification of the World Health Organization (WHO), body mass index (BMI) greater than 25 is considered overweight[3]. An adult who has a BMI of 30 or higher is considered obese. Obesity is further classified into Class I (BMI > 30), Class II (BMI > 35) and Class III (BMI > 40) obesity. In addition to BMI, increased risk of obesity associated metabolic disorders is found in men with waist circumferences greater than or equal to 102 cm and in women with 88 cm[1]. This classification of obesity is primarily based on a Western population perspective[4]. Therefore, it is necessary to redefine obesity from an Asian or Middle Eastern viewpoint. In Asians, overweight has been suggested to start at BMI 23 and also lower waist circumference cut-offs for men and women have been recommended[4].

HEALTH CONSEQUENCES OF OBESITY

Problems related to obesity affects almost every aspect of life[5-6]. The rise in obesity and its complications is a threat to global healthcare system. The obesity epidemic of the world is out of control and none of the current measures show any improvement in reversing this global crisis. Early measures to curb obesity and public awareness on obesity associated diseases are the only way towards

Addresss correspondence to:
Prof. Hussein M. Dashti, Department of Surgery, Faculty of Medicine, PO Box 24923, 13110, Safat, Kuwait. Tel: (965)5319475, Fax: (965)5333098, E-Mail: tcmkwt@gmail.com

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Table 4 Percentage changes in the various parameters after the administration of ketogenic diet for 56 weeks

Change at week 56 (%)	Total (n = 64)	Group I (n = 31) High glucose	Group II (n = 33) Normal glucose	P-value
Weight (kg)	–25.8 ± 6.4	–24.4 ± 6.7	–27.2 ± 6.0	0.3167
Tot. Chol. (mmol/l)	–19.3 ± 17.0	–28.5 ± 11.1	–9.0 ± 16.7	0.0096
HDL (mmol/l)	52.3 ± 43.8	63.4 ± 51.1	39.8 ± 30.0	0.9522
LDL (mmol/l)	–28.2 ± 20.1	–33.0 ± 20.4	–22.9 ± 18.7	0.5467
TG (mmol/l)	–59.0 ± 32.0	–40.8 ± 38.0	–40.8 ± 38.0	0.0039
Glucose (mmol/l)	–31.0 ± 25.0	–50.9 ± 12.5	–7.4 ± 11.9	<0.0001

HDL = high density lipoprotein; LDL = low-density lipoprotein; TG = Triglyceride BMI = body mass index
Data are expressed as mean ± standard deviation. Statistical significance between Group I and Group II are given

Mediterranean diet [35]. It has a protective role in cardiovascular diseases, and various cancers, as well as to diminish the age-related cognitive decline [35–37]. Olive oil is rich in monounsaturated fatty acids and antioxidant substances. The health benefits of olive oil are attributed to these factors. Furthermore, it is shown that olive oil may have protective role for the dynamic blood cholesterol levels in a healthy population [37]. Although olive oil has several beneficial effects, it should be noted that in our previous study [16], we have not included olive oil in the diet and the decrease in weight in obese subjects was similar in both the studies.

A meta-analysis compared the effects of low-carbohydrate diets (maximum carbohydrate intake 60 g daily) with those of low-fat, energy-restricted diets on weight loss [38, 39]. In this meta-analysis, five randomized controlled trials were analyzed, with 6–12 months' duration. It is found that after 6 months, the subjects on a low-carbohydrate diet had lost more weight than those on a low-fat diet. We have noticed a severe weight loss during the initial period as compared to other time points. The overall decrease in weight during the study period (56 weeks) was quite significant. It should be noted that in this study only 20 grams of carbohydrate is given initially and after 12 weeks an additional 20 grams is added to the diet. On the other hand in the above studies [38, 39] the carbohydrate intake was about 60 grams daily. In addition, genetic nature of the population may have influenced these variations.

This study also compared the effect of a low-carbohydrate diet and low-fat diet on the risk factors for cardiovascular disease. It is found that after 6 months, more favorable changes in the level of triglyceride and HDL-cholesterol were observed in the low-carbohydrate group. However, total cholesterol and LDL-cholesterol level changes were more favorable in the low-fat group. In our study, total cholesterol, LDL-cholesterol and triglycerides showed a significant decrease from week 1 to week 56 ($P < 0.0001$), whereas the level of HDL-cholesterol increased significantly ($P < 0.0001$). This again may be due to the difference in carbohydrate intake and the general food habits of the population studied. Furthermore, as mentioned above genetic factors may affect the lipid profile. However, further studies are required to understand the exact mechanisms of the results observed in this study.

Several possible mechanisms on the role of very-low-carbohydrate have been suggested. It is thought that major part of the weight loss following the administration of ketogenic diet could be due to the loss of water. It is also shown that very-low-carbohydrate ketogenic diets may alter the metabolic rate by preserving more lean body mass [40]. There is a greater loss of energy in the form of heat [41] and in the form of ketones in urine, sweat, and feces.

Studies that have assessed body composition on a very-low-carbohydrate ketogenic diet have shown that there is a preferential loss of fat mass and preservation of lean body mass following the administration of ketogenic diet [40, 42, 43]. Prolonged administration of very-low carbohydrate diets did not cause any chronic dehydration [44]. It is generally thought that very-low-carbohydrate diets, especially if high in saturated fat, might lead to insulin resistance. However, contrary to this belief recent studies indicate that very-low carbohydrate diets do not have an adverse effect on glucose metabolism or insulin resistance [45–47].

In conclusion, the data presented in this study shows the beneficial effects of ketogenic diet in obese diabetic subjects following its long-term administration. Furthermore, low-carbohydrate, ketogenic diet (LCKD) may be effective for improving glycemia and reducing medications in patients with type II diabetes.

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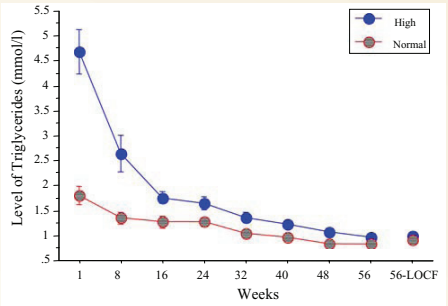

Fig. 5 Changes in the level of tryglycerides after the administration of ketogenic diet for 56 weeks (TG = Triglyceride)

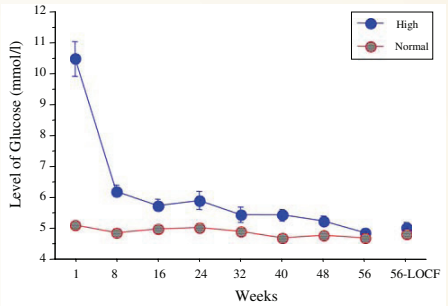

Fig. 6 Changes in the level of blood glucose after the administration of ketogenic diet for 56 weeks

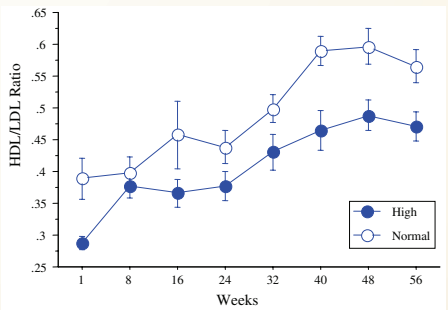

Fig. 7 Changes in HDL/LDL Ratio after the administration of ketogenic diet for 56 weeks (HDL = high density lipoprotein; LDL = low-density lipoprotein)

ketosis may offer therapeutic potential in a variety of different common and rare disease states.

There is an urgent need for identifying effective therapies for obesity, as obesity and obesity associated metabolic disorders have become a serious burden on the health care systems of various countries. Substantial evidence from various studies indicates that very-low-carbohydrate diets are effective for weight loss. As mentioned above, ketogenic diet has been around in the medical literature for well over 70 years [16, 17]. However, several research teams are revisiting very-low-carbohydrate diets to confirm the beneficial claims of ketogenic diet using the current research methodologies and techniques.

This study shows the beneficial effects of ketogenic diet following its long-term administration in obese diabetic and non-diabetic subjects. It significantly reduces the body weight and body mass index. The level of total cholesterol decreased significantly after week 1 until the end of the study. As per the Friedewald formula for LDL cholesterol: LDL-cholesterol = Total cholesterol–(triglycerides/5)–HDL-cholesterol. Thus, Total cholesterol = LDL-cholesterol + HDL-cholesterol + (triglycerides/5) Furthermore, it decreases the level of triglycerides, and LDL-cholesterol. The level of HDL-cholesterol increased significantly in both the groups. The level of triglycerides significantly reduced after. Glucose level decreased significantly. The level of urea showed significant decrease in both the groups. No significant alteration was noticed in renal function test. In this study the HDL/LDL ratio showed a significant increase in both the groups. The LDL/HDL or HDL/LDL ratio is actually a more pure ratio than total cholesterol/HDL. Since LDL is a measure of bad cholesterol and HDL is a measure of good cholesterol, whereas the total cholesterol is the sum of HDL, LDL, and the VLDL.

Most of the studies that dealt with the effect of different diet on obesity [29–33] have clearly shown that people lost more weight on very-low-carbohydrate diets than on diets that contained the same number of calories but more carbohydrates. The only study, to our knowledge that did not demonstrate greater weight loss with the very-low-carbohydrate diet, the energy content of the diet was low (600 kcal/day) and the subjects were >45 kg of body weight [34].

As mentioned in the materials and methods section, most of the subjects were following at least a daily walk of 45 min before participating in this program. However, they have not experienced any reduction in the body weight. In this study, we just allowed them to continue with their routine exercise habits. Thus, we have not introduced a new pattern of exercise together with this diet and obviously, the observed beneficial effects were not related to exercise.

In this study, polyunsaturated and monounsaturated fats (5 tablespoons olive oil) were included in the diet. Olive oil is one of the most characteristic components of

Table 3 Statistical significance between week 1 and week 56 observation of various parameters studied in total, group I (high glucose level) and group II (normal glucose level) subjects

	Group I (n = 31; High Glucose)			Group II (n = 33; Normal Glucose)		
	Week 1	Week 56	P-Value	Week 1	Week 56	P-Value
Weight (kg)	108.081 ± 21.245	83.536 ± 18.030	<0.0001	105.273 ± 15.377	74.923 ± 11.384	<0.0001
Tot. Chol. (mmol/l)	6.755 ± 1.086	4.878 ± 0.533	<0.0001	5.479 ± 1.293	4.650 ± 0.495	0.0020
HDL (mmol/l)	1.033 ± 0.264	1.586 ± 0.211	<0.0001	1.237 ± 0.270	1.621 ± 0.177	<0.0001
LDL (mmol/l)	5.160 ± 0.892	3.379 ± 0.608	<0.0001	4.030 ± 1.148	2.807 ± 0.496	<0.0001
TG (mmol/l)	4.681 ± 2.468	1.006 ± 0.205	<0.0001	1.827 ± 0.981	0.861 ± 0.179	0.0001
Glucose (mmol/l)	10.481 ± 3.026	4.874 ± 0.556	<0.0001	5.127 ± 0.440	4.726 ± 0.529	0.0069
Urea (μmol/l)	5.778 ± 0.905	4.972 ± 1.050	0.0111	5.563 ± 1.299	4.419 ± 0.743	<0.0001

HDL = high density lipoprotein; LDL = low-density lipoprotein; TG = Triglyceride BMI = body mass index

Data are expressed as mean ± standard deviation

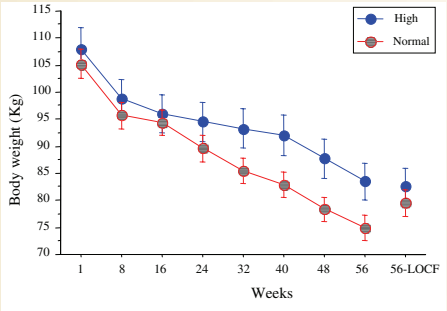

Fig. 1 Changes in body weight after the administration of ketogenic diet for 56 weeks

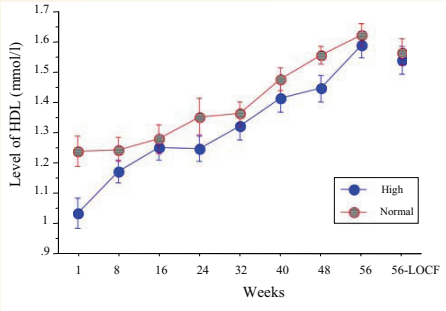

Fig. 3 Changes in the level of HDL after the administration of ketogenic diet for 56 weeks. (HDL = high density lipoprotein)

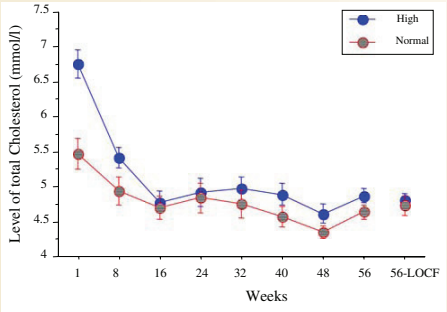

Fig. 2 Changes in the level of total cholesterol after the administration of ketogenic diet for 56 weeks

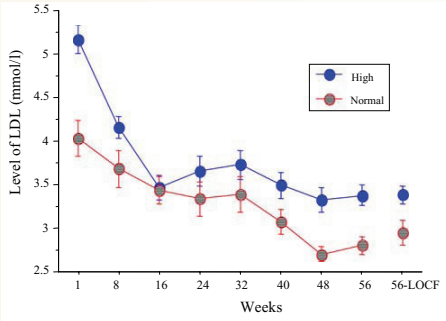

Fig. 4 Changes in the level of LDL after the administration of ketogenic diet for 56 weeks (LDL = low-density lipoprotein)

anti-convulsants at controlling seizures. In a recent study [28], ketone bodies have been used as therapeutic agents for the treatment of: (a) diseases of substrate insufficiency or insulin resistance, (b) diseases resulting from free radical damage, and (c) disease resulting from hypoxia. These studies on ketone body metabolism suggest that mild

Table 2 Recommended and restricted food in ketogenic diet

Recommended food			Fully restricted food	
Proteins	Vegetables/Fruits	Oil	Carbohydrates	Fruits/ drinks
Fish: Tuna, Sardine Prawns, Shrimps. Lobster	Spinach, Watercress, Eggplant, Parsley, Mulberry, Coriander, Mint, Artichoke, Okra, Cabbage, Mushroom, Avocado, Leek, Carrot, Radish, Celery, Cauliflower, Green pepper, Lettuce, Cucumber, Tomato, 10–15 olives/ day, Lemon, Strawberry -6/day, Avocado, Berries-10/day	Olive oil (5 tablespoon) added to the salad, Flax seed oil	Flour, Potato, Macaroni Spaghetti, Noodles, Bread, Rice, Sugar, Sweets, Honey, Cakes	All fruit juices, all soft drinks
Meat: Kababs, Sausages, Minced				
Poultry: Chicken, Eggs				
Cheese: Full fat cheese				

cheese. The subjects in this study were not consuming any kind of alcoholic beverages. Polyunsaturated and monounsaturated fats (5 tablespoons olive oil) were included in the diet. A list of recommended and restricted food in ketogenic diet is given in Table 2. Twelve weeks later an additional 20 g of carbohydrates was given. Micronutrients (vitamins and minerals) in the form of 1 capsule/day were given to each subject throughout the study period.

Fasting blood tests were carried out in all the subjects. The subjects were subjected to liver and renal function tests, complete blood count, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL; directly measured), triglycerides (TG), urea and creatinine in the beginning after 8, 16, 24, 32, 40, 48 and 56 weeks. Biochemical analysis of lipid, liver, renal profiles and electrolytes were performed by Beckman CX 5 C E and complete blood count was carried out by Coulter MD II. The body mass index (the weight in kilograms divided by square of the height) was determined initially and after 8, 16, 24, 32, 40, 48 and 56 weeks. We standardized our results with daily internal and external quality control program with ''Lab quality Finland.'' During each visit, enquiries were made regarding their adherence to the diet, exercise habits and any side effects or uncomfortable feelings they felt.

Most of the subjects as advised by their General Practitioners were following at least a daily walk of 45 min before participating in this program and we allowed them to continue with their routines.

Statistical differences between different parameters before and after the administration of ketogenic diet were analyzed by student-*t* test using a computer software package (Stat view 4.02). Age, weight and all biochemical parameters were expressed as mean ± standard deviation.

Results

Statistical significance between week 1 and week 56 observation of various parameters studied in total, group I (high blood glucose level) and group II (normal blood glucose level) subjects is given in Table 3. There was a significant reduction in the body weight (Fig. 1) in Group I (high blood glucose) and Group II (normal blood glucose) throughout the program. The effect of gender in body weight was not significant. The level of total cholesterol decreased significantly after week 1 until the end of the study (Fig. 2). HDL-cholesterol increased significantly (Fig. 3), whereas LDL-cholesterol decreased significantly (Fig. 4). The level of triglycerides significantly decreased from the start till the end of the study (Fig. 5). The blood glucose level of both the groups decreased significantly from the start until the 56th week (Fig. 6). HDL/LDL ratio (Fig. 7) showed a significant increase in both the groups ($P < 0.0001$). The data in Figs. 1–7 are expressed as mean ± standard error. Percentage changes at the end of the study (56 weeks) in the various parameters observed are given in Table 4. There was a significant decrease in urea at week 1 and week 56 (Table 3). The changes in the level of creatinine were not statistically significant.

Discussion

Ketosis is a natural phenomenon that occurs in man during fasting and lactation. Administration of this diet mimics the effects of starvation. Ketogenic diet has been around in the medical literature for well over 70 years [16, 17], especially as an effective treatment for controlling seizures. In some instances it is actually better than the modern

II diabetes and obesity to occur together [6–9]. Type II diabetes is characterized by impaired insulin sensitivity (resistance) coupled with the inability of the pancreatic β-cells to produce adequate amount of insulin depending on the increased demand. Obesity is known to aggravate insulin resistance and is an early metabolic defect in nearly all individuals with type II diabetes [10]. Type I diabetes on the other hand is developed by the deficiency of insulin due to destruction of pancreatic β-cells. High blood glucose level leads to complications of vasculopathy, retinopathy, nephropathy, neuropathy, and cardiomyopathy [11, 12].

Although the exact molecular mechanism that link obesity to diabetes needs to be elucidated, one of the causes of metabolic syndrome may be the ectopic accumulation of lipids. Although, adipose tissue is the primary organ of lipid storage, in obese subjects, lipid is deposited into other non-adipose organs, such as liver, skeletal muscle, β-cells, and cardiac tissue. The ectopic lipid deposited in the liver leads to the commonly observed hepatic steatosis or fatty liver. Lipid deposition in skeletal muscle and β -cells leads to insulin resistance, impaired insulin secretion, and eventually type II diabetes [13].

Various studies have shown that reducing weight in obese patients with glucose intolerance, have beneficial effects in delaying or even preventing the progression to diabetes. Thus, effective management of body weight and changes to nutritional habits have beneficial effects in obese diabetic subjects [14, 15]. However, the ideal nature of weight reducing diet program for patients with impaired insulin sensitivity is quite debatable and needs careful monitoring.

Recent studies from our laboratory [16–18] have shown the beneficial effects of ketogenic diet in which the daily consumption of carbohydrate is less than 20 g, regardless of fat, protein, and caloric intake, in overweight and obese patients. We have shown that in addition to reducing the weight in overweight and obese individuals, it reduces the risk factors for cardiovascular diseases even in hyperlipidemic obese subjects [16–18] as compared to other diet programs [19–25].

It is quite logical to assume that excessive intake of carbohydrate may be harmful to individuals with insulin resistance. Following the consumption of a large amount of carbohydrate, there was an obvious increase in the level of blood glucose, insulin, and serum triglycerides in insulin-resistant individuals. In addition, a high carbohydrate diet raises triglyceride levels and reduces HDL-cholesterol along with insulin resistance [26, 27].

Considering the above-mentioned disorders associated with the intake of a high-carbohydrate diet in obese subjects, the purpose of this study was to monitor the changes in body weight, lipid profile, glucose, urea, and creatinine following the administration of a low-carbohydrate, ketogenic diet (LCKD) in overweight and obese diabetic subjects as compared to non-diabetic obese subjects for a period of 56 weeks.

Materials and methods

In this study, 64 healthy obese subjects with body mass index (BMI) greater than 30, having blood glucose level >6.1 mmol/l (Group I; $n = 31$) and those subjects with normal blood glucose level (Group II; $n = 33$) were selected. Subjects with other complex medical histories were not included in this study. The body weight, blood glucose level, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, urea, and creatinine were determined before and at 8, 16, 24, 48, and 56 weeks after the administration of the ketogenic diet. Their average age, body weight, and base line parameters of other biochemical parameters are given in Table 1. All the subjects included in this study were Kuwaitis, with similar dietary habits.

All 64 subjects were instructed to follow a ketogenic diet consisting of less than 20 g of carbohydrates and 80–100 g of proteins in the form of meat, fish, fowl, eggs, shellfish, and

Table 1 Baseline values of different physical and biochemical parameters monitored in persons subjected to low-carbohydrate diet (ketogenic diet)

	Group I ($n = 31$) High glucose	Group II ($n = 33$) Normal glucose	P-value
Age (years)	46.4 ± 9.4	40.0 ± 11.4	0.1197
Weight (kg)	108.1 ± 21.2	105.3 ± 15.4	0.5349
Tot. Chol. (mmol/l)	6.8 ± 1.1	5.5 ± 1.3	0.0003
HDL (mmol/l)	1.0 ± 0.3	1.2 ± 0.3	0.0552
LDL (mmol/l)	5.2 ± 0.9	4.0 ± 1.1	0.0002
TG (mmol/l)	4.7 ± 2.5	1.8 ± 1.0	<0.0001
Glucose (mmol/l)	10.5 ± 3.0	5.1 ± 0.4	<0.0001

HDL = high density lipoprotein; LDL = low-density lipoprotein; TG = Triglyceride

Data are expressed as mean ± standard deviation

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البحث الرابع

Beneficial effects of ketogenic diet in obese diabetic subjects

Hussein M. Dashti · Thazhumpal C. Mathew · Mousa Khadada · Mahdi Al-Mousawi · Husain Talib · Sami K. Asfar · Abdulla I. Behbahani · Naji S. Al-Zaid

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Abstract
Objective Obesity is closely linked to the incidence of type II diabetes. It is found that effective management of body weight and changes to nutritional habits especially with regard to the carbohydrate content and glycemic index of the diet have beneficial effects in obese subjects with glucose intolerance. Previously we have shown that ketogenic diet is quite effective in reducing body weight. Furthermore, it favorably alters the cardiac risk factors even in hyperlipidemic obese subjects. In this study the effect of ketogenic diet in obese subjects with high blood glucose level is compared to those with normal blood glucose level for a period of 56 weeks.
Materials and methods A total of 64 healthy obese subjects with body mass index (BMI) greater than 30, having high blood glucose level and those subjects with normal blood glucose level were selected in this study. The body weight, body mass index, blood glucose level, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, urea and creatinine were determined before and at 8, 16, 24, 48, and 56 weeks after the administration of the ketogenic diet.
Results The body weight, body mass index, the level of blood glucose, total cholesterol, LDL-cholesterol, triglycerides, and urea showed a significant decrease from week 1 to week 56 ($P < 0.0001$), whereas the level of HDL-cholesterol increased significantly ($P < 0.0001$). Interestingly these changes were more significant in subjects with high blood glucose level as compared to those with normal blood glucose level. The changes in the level of creatinine were not statistically significant.
Conclusion This study shows the beneficial effects of ketogenic diet in obese diabetic subjects following its long-term administration. Furthermore, it demonstrates that in addition to its therapeutic value, low carbohydrate diet is safe to use for a longer period of time in obese diabetic subjects.

Keywords Obesity · Blood glucose · Cholesterol · LDL · HDL · Triglycerides · Low-carbohydrate diet · Ketogenic diet

H. M. Dashti (✉) · S. K. Asfar · A. I. Behbahani
Departments of Surgery, Faculty of Medicine, Kuwait University, PO Box 24923, 13110 Safat, Kuwait
e-mail: info@drdashti.com

T. C. Mathew
Faculty of Medicine and Faculty of Allied Health Sciences, Kuwait University, Safat, Kuwait

M. Khadada
Department of Medicine, Kuwait University, Safat, Kuwait

M. Al-Mousawi · H. Talib
Primary Health Care Salmeiah and Shaab Clinic, Kuwait University, Safat, Kuwait

N. S. Al-Zaid
Department of Physiology, Kuwait University, Safat, Kuwait

Introduction

Obesity is a serious universal health problem [1, 2]. In the United States, two of every three adults are either overweight (BMI of 25–29.9 kg/m^2) or obese (BMI of 30 and above; [3]). Similarly, there is a tremendous increase in the rate of obesity in Kuwait and other Gulf countries. During the last decade there is a high prevalence of obesity in Kuwait [4, 5].

Obesity substantially increases the risk of morbidity from various chronic diseases. There is a tendency for type

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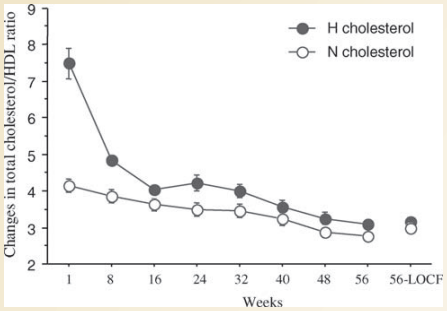

Fig. 12. Total cholesterol/ HDL ratio in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 32, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. $^{*}p$ Value <0.0001 compared with week 1.

and risk factors associated with various chronic diseases [1, 25–29].

These studies show the beneficial effects of ketogenic diet following its long term administration. It significantly reduces the body weight and body mass index. Furthermore, it decreases the level of triglycerides, and LDL-cholesterol [26–29].

The data presented in this study shows that both high and normal cholesterol groups showed reduction of LDL, however, there was no significant alteration between genders. The level of triglycerides significantly reduced after 8 weeks and showed a further gradual decrease in both groups till the end of the year. Similar changes occurred in males and females. Glucose level decreased significantly in both groups in males and females. As there were no significant differences in male and female subjects in all the parameters examined, the data of males and females in each group are pooled and presented together.

Majority of the subjects who attended the Consultation and training office in the Faculty of Medicine, Kuwait University, suffered from metabolic syndrome (visceral obesity, atherogenic dyslipedemia (i.e low level of high density lipoprotein and elevation of total cholesterol and triglyceride) and elevation of blood sugar. Various investigators have convincingly shown that triglyceride-rich lipoprotein plays a major role in atherogenesis [30–34] and fasting triglyceride is directly related to cardiovascular disease [35, 36], myocardial infarction, hypertension and diabetes mellitus [37, 38].

Ratio of total cholesterol/HDL and LDL/HDL are used as predictors of cardiac disease. Recent studies have shown that an increase in one unit in the LDL/HDL ratio and an increase in total cholesterol /HDL ratio is associated with a 53% [39, 40] and 49% [27], increase in the risk of myocardial infarction, respectively. In another study it is found that an increase in the ratio of LDL to HDL by one unit may even contribute to a 75% increase in the risk of myocardial infarction [38].

Unfortunately, one of the limitations of this study was that we were unable to estimate the fasting insulin level in these subjects. However, there was obvious improvement in their blood sugar level. In a similar study with low carbohydrate diet, Noakes *et al.* [41] have shown a 33% decrease in fasting insulin level along with improvement of fasting glucose level, blood pressure and reduction in body weight.

Other investigators have also shown that low carbohydrate diet had an influence in decreasing fasting triglyceride as well as the ratio of triglyceride to high density lipoprotein and improvement in blood sugar along with reduction in body weight [42–44]. Although, these studies did not compare the effects of ketogenic diet in subjects with hypercholesterolemia to those with normocholesterolemia, these studies collectively indicate that a low carbohydrate diet had more favourable outcomes with regard to weight and lipid profile than those who were on a conventional diet.

Regarding exercise most of the subjects as advised by their General Practitioners were following at least a daily walk of 45 min before participating in this program. However, they have not experienced any reduction in body weight. Thus, we have not introduced a new pattern of exercise together with this diet. On the other hand we just allowed them to continue with their routines. It should be noted that we have included about 5 tablespoons olive oil in the diet recommended to the participants in this programme. Historically, olive oil is one of the most characteristic components of Mediterranean diet [45]. It has a protective role in cardiovascular diseases, and various cancers, as well as to diminish the age-related cognitive decline [45–47]. Olive oil is rich in monounsaturated fatty acids and antioxidant substances. The health benefits of olive oil are attributed to these factors. Furthermore, it is shown that olive oil may have protective role for the dynamic blood cholesterol levels in a healthy population [47]. It should be noted that in our previous study [1], we have not included olive oil in the diet and the decrease in weight in obese subjects was similar in both the studies.

Administering ketogenic diet for a relatively longer period did not produce any significant side effects in subjects with high level of total cholesterol. Therefore, this study suggests that it is safe to use ketogenic diet for a longer period of time regardless of the total cholesterol level of the subjects.

Acknowledgments

We would like to thank Dr. J. Longnecker, Department of Community Medicine, Faculty of Medicine, Kuwait University for expert statistical consultation.

Table 6. Statistical significance between week 1 and week 56 observation of various parameters studied in total, group I and group II subjects

	Total	Group I ($n = 35$; High cholesterol)	Group II ($n = 31$; Normal cholesterol)
Weight (Kg)	<0.0001	<0.0001	<0.0001
BMI (Kg/m^2)	<0.0001	<0.0001	<0.0001
Tot.Chol. (mmol/l)	<0.0001	<0.0001	0.0170
HDL (mmol/l)	<0.0001	<0.0001	<0.0001
LDL (mmol/l)	<0.0001	<0.0001	<0.0001
TG (mmol/l)	<0.0001	<0.0001	0.0002
Glucose (mmol/l)	<0.0001	<0.0001	0.0034

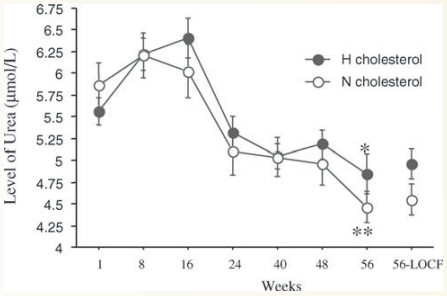

Fig. 8. Changes in the level of urea in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1 in hypercholesterolemic subjects. **p Value 0.0131 compared with week 1 in normocholesterolemic subjects.

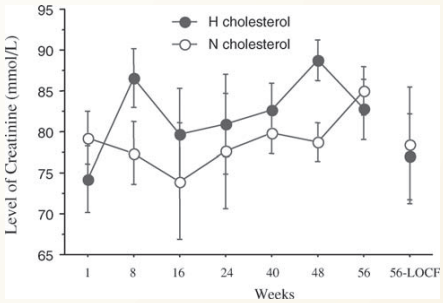

Fig. 9. Changes in the level of creatinine in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward.

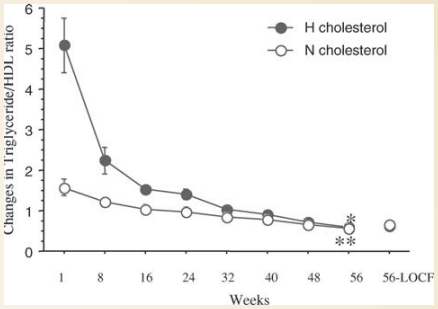

Fig. 10. Triglyceride/HDL ratio in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1 in hypercholesterolemic subjects. **p Value 0.0001 compared with week 1 in normocholesterolemic subjects.

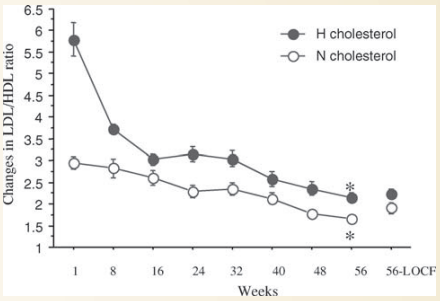

Fig. 11. LDL/HDL ratio in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 32, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1.

is associated with a variety of chronic diseases. It is estimated that in United States alone about 300,000 people die each year from obesity related diseases. There is a gradual increase in the number of obese people in United States [21–24]. A similar trend is observed in Kuwait and other Middle East countries. The different attempts for reducing weight by reduced calorie and fat intake combined with exercise have failed to show a sustained long term effect. Recent studies from various laboratories, including ours have shown that a high fat diet rich in polyunsaturated fatty acids (ketogenic diet) is quite effective in reducing body weight

Table 5. Percentage changes in the various parameters observed at week 56 in persons subjected to ketogenic diet

	Total ($N = 66$)	Group I ($N = 35$; High cholesterol)	Group II ($N = 31$; Normal cholesterol)	p-value
Weight (Kg)	−25.9 ± 6.3	−25.8 ± 6.7	−26.0 ± 5.8	0.9065
Tot.Chol. (mmol/l)	−19.3 ± 17.0	−29.2 ± 9.4	−6.2 ± 16.2	0.0005
HDL (mmol/l)	52.3 ± 43.8	63.7 ± 52.7	37.1 ± 20.6	0.1778
LDL (mmol/l)	−28.2 ± 20.1	−33.5 ± 19.5	−21.3 ± 19.1	0.1331
TG (mmol/l)	−59.0 ± 32.1	−69.8 ± 32.6	−44.7 ± 25.7	0.0537
Glucose (mmol/l)	−31.0 ± 25.0	−44.0 ± 22.6	−12.8 ± 15.1	0.0004

HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglyceride BMI: Body mass index; Tot.Chol.: Total cholesterol.
Data is expressed as mean ± standard deviation. Statistical significance between Group I and Group II are given.

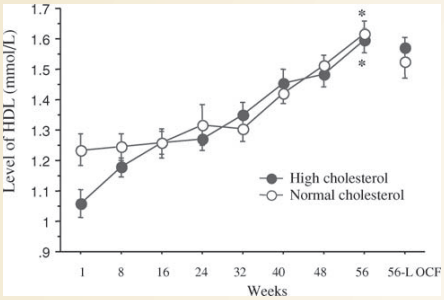

Fig. 4. Changes in the level of HDL-cholesterol expressed as mean ± SEM, following treatment with ketogenic diet in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia for a period of 56 weeks. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1.

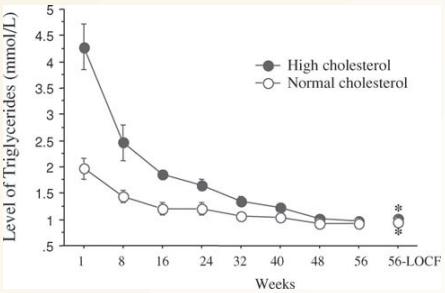

Fig. 6. Changes in the level of triglycerides in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia following treatment with ketogenic diet in obese subjects at 8, 16, 24, 32, 40, 48 and 56 weeks. The levels of triglycerides are expressed as mean ± SEM. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1.

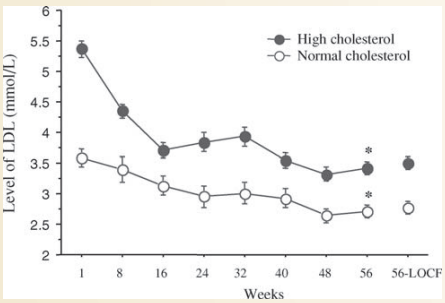

Fig. 5. Changes in the level of LDL-cholesterol following treatment with ketogenic diet at 8, 16, 24, 32, 40, 48 and 56 weeks in obese subjects with high level of cholesterol as compared to those with normal level of cholesterol. The levels of LDL-cholesterol are expressed as mean ± SEM. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1.

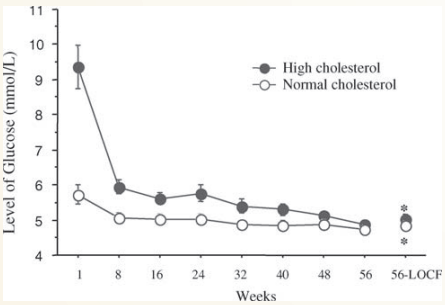

Fig. 7. Decreased levels of glucose expressed as mean ± SEM following the administration of ketogenic diet in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia at 8, 16, 24, 40, 48 and 56 weeks. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1.

Table 4. Baseline values of different physical and biochemical parameters monitored in persons subjected to low carbohydrate diet (ketogenic diet)

	Total	Group I ($n = 35$)	Group II ($n = 31$)	p-value
Age (years)	42.9 ± 10.8	45.5 ± 9.2	39.9 ± 11.8	0.0731
Weight (Kg)	106.9 ± 18.3	112.3 ± 19.3	100.7 ± 15.3	0.0168
BMI (Kg/m^2)	39.1 ± 6.1	40.1 ± 6.1	38.0 ± 6.1	0.1385
Tot.Chol. (mmol/l)	6.1 ± 1.4	7.0 ± 0.9	5.0 ± 0.8	<0.0001
HDL (mmol/l)	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	0.0076
LDL (mmol/l)	4.6 ± 1.2	5.4 ± 0.8	3.6 ± 0.7	<0.0001
TG (mmol/l)	3.2 ± 2.3	4.3 ± 2.6	2.0 ± 1.1	<0.0001
Glucose (mmol/l)	7.7 ± 3.4	9.4 ± 3.7	5.7 ± 1.5	<0.0001

HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglyceride BMI: Body mass index; Tot.Chol.: Total cholesterol.
Data is expressed as mean ± standard deviation.

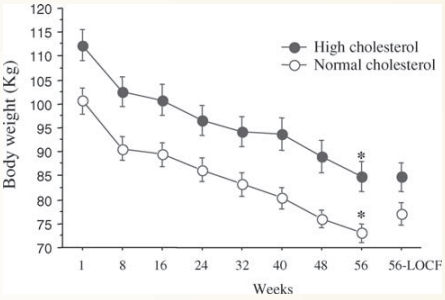

Fig. 1. Reduction in body weight at 8, 16, 24, 32, 40, 48 and 56 weeks following the administration of ketogenic diet in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia. The weights are expressed as mean ± SEM. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1.

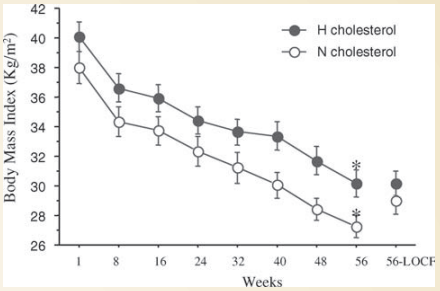

Fig. 2. Reduction in body mass index (BMI) at 8, 16, 24, 32, 40, 48 and 56 weeks following the administration of ketogenic diet in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia. The BMI are expressed as mean ± SEM. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1.

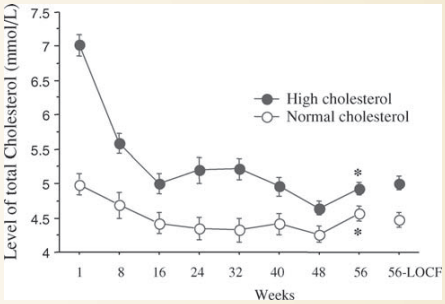

Fig. 3. Decreased levels of total cholesterol expressed as mean ± SEM, in obese subjects with hypercholesterolemia as compared to those with normocholesterolemia at 8, 16, 24, 32, 40, 48 and 56 weeks following the administration of ketogenic diet. LOCF; Last observation carried forward. *p Value <0.0001 compared with week 1.

and females in both Group I (high cholesterol) and Group II (normal cholesterol) throughout the program (Fig. 2).

There was a significant change ($P < 0.0001$) in the lipid profile of the subjects during the entire study period. The level of total cholesterol decreased significantly after week 1 until the end of the study (Fig. 3). HDL-cholesterol increased significantly (Fig. 4), whereas LDL-cholesterol decreased significantly (Fig. 5). The level of triglycerides significantly decreased from the start till the end of the study (Fig. 6). The blood glucose level of males and females decreased significantly ($P < 0.0001$) from the start until the 56th week (Fig. 7).The percentage changes in the various parameters observed at the end of the study and the statistical significance between week one and week 56 observations in total, group I and group II subjects are given in Tables 5 and 6 respectively. The changes in the level of urea and creatinine at week 1 and week 56 are given in Figs. 8 and 9 respectively. The changes in the levels of urea were statistically significant while changes in the levels of creatinine were not significant. The ratio of triglyceride/HDL, LDL/HDL and total cholesterol/HDL at week 1 and week 56 are given in Figs. 10, 11 and 12 respectively.

Discussion

Obesity has become a serious chronic disease in both developing and developed countries [21–24]. Furthermore, it

Table 1. Recommended and restricted food in ketogenic diet

Recommended food			Fully restricted food	
Proteins	Vegetables/Fruits	Oil	Carbohydrates	Fruits/drinks
Fish: Tuna, Sardine Prawns, Shrimps. Lobster	Spinach, Watercress, Eggplant, Parsley, Mulberry, Coriander, Mint, Artichoke, Okra, Cabbage, Mushroom, Avocado, Leek, Carrot, Radish, Celery, Cauliflower, Green pepper, Lettuce, Cucumber, Tomato, 10–15 olives/day, Lemon	Olive oil (5 tablespoon, added to the salad	Flour, Potato, Macaroni Spaghetti, Noodles, Bread, Rice, Sugar, Sweets, Honey, Cakes	All fruit juices
Meat: Kababs, Sausages, Minced	Strawberry-6/day, Avocado	Flax seed oil		All soft drinks
Poultry: Chicken, Eggs	Berries-10/day			
Cheese: Full fat cheese				

Table 2. Composition of the capsule containing micronutrients

Vit. A	1000 IU
Beta-Carotene	3000 IU
Vit E	75 IU
Vit C	90 mg
Folic Acid	0.6 mg
Vit. B1	2.25 mg
Vit. B2	3.2 mg
Niacinamide	15 mg
Vit. B6	8 mg
Vit. B12	25 mg
Vit D	400 IU
BIOTIN	45 mcg
Pantathenic acid	10 mg
Minerals	
Calcium	200 mg
Phosphorus	125 mg
Iodine	0.15 mg
Iron	4 mg
Magnesium	50 mg
Copper	2 mg
Manganese	5 mg
Pottassium	80 mg
Chlorine	72 mg
Chromium	100 mcg
Malybdenum	25 mcg
Selenium	25 mcg
Zinc	15 mg
Nickel	5 mcg
Tin	0.010 mg
Vanadium	10 mcg
Silicon	0.010 mg
Other Ingredients	
Lutein	250 mg

Source: Centrum Select, Canada.

visit, enquiries were made regarding their adherence to the diet, exercise habits and any side effects or uncomfortable feelings they felt.

Statistical differences between parameters before and after the administration of ketogenic diet were analyzed by ANOVA and student- t test using a package (Stat view 4.02). Age, body mass index and all biochemical parameters were expressed as mean ± standard error.

Results

Among the 66 subjects who were included in this study, 35 subjects belonged to group I and 31 to group II. Their age ranged from 17 to 67. Only 49 subjects (74%) completed 56 weeks successfully. At 56 weeks, there were 26 subjects in group I (with high cholesterol level) and 23 in group II (with normal cholesterol level). Among the 49 subjects who completed the study, 25 were male and 24 were female subjects (Table 3).

The average age, weight, BMI and the baseline values of other biochemical parameters examined in this study are given in Table 4. There was a significant reduction ($P < 0.0001$) in the body weight (Fig. 1) and the BMI of males

Table 3. Number of patients at different stages of the study

	Group I (High Cholesterol) *N* (%)	Group II (Normal Cholesterol) *N* (%)	Total *N* (%)
Week-1	35 (100)	31 (100)	66 (100)
Week-24	34 (97.1)	28 (90.3)	62 (93.9)
Week-32	32 (91.4)	27 (87.1)	59 (89.4)
Week-40	30 (85.7)	26 (83.9)	56 (84.8)
Week-56	26 (74.3)	23 (74.2)	49 (74.2)

In this study a low carbohydrate diet (Ketogenic diet) in which the daily consumption of carbohydrate is less than 20 g, regardless of fat, protein and caloric intake is used. In subjects with ketogenic diet, the metabolic energy requirements are obtained from the adipose tissue and/or from dietary fat consumed by the subject. The ketone bodies, acetoacetic acid, β-hydroxybutyrate and acetone produced during the fat metabolism substitute for glucose in subjects with ketogenic diet. Furthermore, 1 g of protein can give away 0.5 g of glucose whenever patient is on ketogenic diet [4], thus it sustains positive nitrogen balance and ultimately preserves the lean body mass [5].

Currently, there is a wide popularity about ketogenic diet, prompting concerns regarding the use of ketogenic diet in weight reductions programs. However, very few studies evaluated their effect in cardiac risk factors [6, 7]. These studies indicated that application of ketogenic diet results in significant decrease in serum triglycerides, small increase in total and LDL cholesterol and moderate increase in HDL cholesterol in subjects with normal lipid profile. In another study it is shown that for every kilogram of weight loss, HDL cholesterol increases 0.009 and triglycerides decrease 0.015 mmol/L [8]. Elevated fasting triglyceride is found to be an independent risk factor for cardiovascular diseases [9]. On the other hand, numerous studies suggest that a high carbohydrate diet raise triglyceride levels and reduce HDL cholesterol along with insulin resistance [10, 11]. Interestingly, these changes in triglyceride and HDL levels were reversed by replacing saturated fat instead of carbohydrate [12, 13].

Considering the complications caused by high cholesterol level in the blood, the usual tendency is to modify the diet so as to eliminate cholesterol and unsaturated fat. In this regard, it is reasonable to believe that the best alternative in such a situation is to enable the cells to use excess lipids to produce energy, which also reduces obesity. The cells can be primed to this type of metabolism by using a high fat diet and by not providing carbohydrate, which is the usual source of fuel for the energy requirements in the body. Various studies have convincingly shown the beneficial effects of ketogenic diet in reducing weight in obese subjects as compared to other diet programs [14–20], its long term effect on the lipid profile of obese subjects with high total cholesterol as compared to obese subjects with normal cholesterol level is lacking. Therefore, the present study was carried out to demonstrate the changes in body weight, lipid profile, glucose, urea and creatinine that might occur after the administration of ketogenic diet throughout the period of study (56 weeks), in healthy obese subjects with hypercholesterolemia as compared to those obese subjects with normocholesterolemia.

Materials and methods

Obese subjects (BMI greater than 30) who attended the Consultation and training office in the Faculty of Medicine, Kuwait University, were included in the study. Medical history and clinical examination were carried out on all the subjects during each visit. Among the 997 obese subjects who attended the Consultation and training office, only 66 subjects (34 males and 32 females) were included in this study. 119 subjects refused to participate in this study, whereas 812 subjects who were suffering from other health related problems such as heart diseases, hepatic diseases, serum creatinine above 120 μmol/L and with history of weight loss medication were excluded from the study. All the subjects who were included in this study were Kuwaitis. The subjects were divided into two groups: Group I (21 males and 14 females), subjects with high cholesterol level above 6 mmol/L (normal 3.4–6.00 mmol/L); and Group II (13 males and 18 females), subjects with normal cholesterol level less than 6 mmol/L. Among the 66 subjects included in the study, 35 subjects belonged to Group I and 31 to Group II.

All 66 subjects received a ketogenic diet consisting of less than 20 g of carbohydrates in the form of green vegetables and salad and 80–100 g of proteins in the form of meat, fish, fowl, eggs, shellfish and cheese. Polyunsaturated and monounsaturated fats (5 tablespoons olive oil) were included in the diet. Gradually, the amount of carbohydrate is raised from the original 20 to 40 g in order to supply sufficient glucose to sustain the cells with few or no mitochondria such as erythrocytes, cornea, lens, renal medulla and leukocytes [4].

A list of recommended and restricted food in ketogenic diet is given in Table 1. In addition, micronutrients (vitamins and mineral; Centrum Select, Canada) in the form of 1 capsule/day were given to each subjects (Table 2). Twelve weeks later an additional 20 g of carbohydrate was given. During each visit, participants were asked regarding the adherence to the diet and adverse effects. All participants were asked to perform exercise in the form of 45 min walking daily.

Fasting blood tests were carried out in all the subjects. The subjects were subjected to liver and renal function tests, complete blood count, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL; directly measured), triglycerides (TG), urea and creatinine in the beginning after 8, 16, 24, 32, 40, 48 and 56 weeks. Biochemical analysis of lipid, liver, renal profiles and electrolytes were performed by Beckman CX 5 C E and complete blood count was carried out by Coulter MD II. The body mass index (the weight in kilograms divided by square of the height) was determined initially and after 8, 16, 24, 32, 40, 48 and 56 weeks. We standardized our results with daily internal and external quality control program with “Lab quality Finland”. During each

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البحث الثالث

Long term effects of ketogenic diet in obese subjects with high cholesterol level

Hussein M. Dashti,[1] Naji S. Al-Zaid,[2] Thazhumpal C. Mathew,[3] Mahdi Al-Mousawi,[4] Hussain Talib,[4] Sami K. Asfar[1] and Abdulla I. Behbahani[1]

[1]*Department of Surgery, Kuwait University, Kuwait;* [2]*Department of Physiology, Kuwait University, Kuwait;* [3]*Faculty of Medicine and Faculty of Allied Health Sciences, Kuwait University, Kuwait;* [4]*Primary Health Care Salmeiah and Shaab Clinic*

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Abstract

Objective: Various studies have convincingly shown the beneficial effect of ketogenic diet (in which the daily consumption of carbohydrate is less than 20 grams, regardless of fat, protein and caloric intake) in reducing weight in obese subjects. However, its long term effect on obese subjects with high total cholesterol (as compared to obese subjects with normal cholesterol level) is lacking. It is believed that ketogenic diet may have adverse effect on the lipid profile. Therefore, in this study the effect of ketogenic diet in obese subjects with high cholesterol level above 6 mmol/L is compared to those with normocholesterolemia for a period of 56 weeks.

Materials and methods: In this study, 66 healthy obese subjects with body mass index (BMI) greater than 30, having high cholesterol level (Group I; $n = 35$) and those subjects with normal cholesterol level (Group II; $n = 31$) were selected. The body weight, body mass index, total cholesterol, LDL-cholesterol, HDL-cholesterol, urea, creatinine, glucose and triglycerides were determined before and after the administration of the ketogenic diet. Changes in these parameters were monitored at 8, 16, 24, 32, 40, 48 and 56 weeks of the treatment.

Results: The body weight and body mass index of both groups decreased significantly ($P < 0.0001$). The level of total cholesterol, LDL cholesterol, triglycerides and blood glucose level decreased significantly ($P < 0.0001$), whereas HDL cholesterol increased significantly ($P < 0.0001$) after the treatment in both groups.

Conclusion: This study shows the beneficial effects of ketogenic diet following its long term administration in obese subjects with a high level of total cholesterol. Moreover, this study demonstrates that low carbohydrate diet is safe to use for a longer period of time in obese subjects with a high total cholesterol level and those with normocholesterolemia. (Mol Cell Biochem **286:** 1–9, 2006)

Key words: blood glucose, cholesterol, HDL, ketogenic diet, LDL, low carbohydrate diet, obesity, triglycerides

Introduction

Ketogenic diet has been around in the medical literature for well over 70 years [1]. It has been known that fasting has beneficial effects on seizure control. For many years, it was used as an anti-convulsant for controlling seizures. In some cases it is actually better than the modern anti-convulsants at controlling seizures. Mild ketosis is a natural phenomenon that occurs in man during fasting and lactation. Post-exercise ketosis is a well known phenomenon in mammals, the diet mimics the effects of starvation [1–3].

Address for offprints: H.M. Dashti, Department of Surgery, Faculty of Medicine, P.O. Box 24923, 13110, Safat, Kuwait (E-Mail: info@drdashti.com)

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selective antineoplastic therapy. The supply of substrates for tumour energy metabolism can be reduced by dietary manipulation (eg, ketogenic diet) or by pharmacological means at the cellular level (eg, inhibitors of glycolysis or oxidative phosphorylation). Both of these techniques are nontoxic methods for controlling tumour growth in vivo (61). Sugar consumption is positively associated with cancer in humans and test animals (58-61). This observation is quite logical because tumours are known to be enormous sugar absorbers. It has also been found that the risk of breast cancer decreases with increases in total fat intake (16). Further studies on the role of a ketogenic diet in antineoplastic therapy are in progress in our laboratory.

A link between low fat diets and osteoporosis has been suggested. Very low fat diets are considered to be low in calcium content. Women on low fat diets excrete most of the calcium they consume; therefore, they are more prone to osteoporosis. However, a high fat diet can rectify this situation (62).

In the present study, a control population on a low fat diet was not included due to the difficulties in recruiting subjects for a control group. However, several studies (63,64) with appropriate control groups that compared the effect of a low fat diet with a low carbohydrate ketogenic diet have recently been published. In this regard, these two recent studies are comparable with the present study. Brehm et al (23) showed that obese women on a low carbohydrate ketogenic diet lost 8.5 kg over six months compared with 4.2 kg lost by those in the low fat diet group ($P<0.001$). Twenty-two subjects from the low carbohydrate ketogenic diet and 20 subjects from the low fat diet completed the study, with both groups reducing their energy intake by approximately 450 kcal from the baseline level. In another study performed in 132 severely obese subjects for six months (24), there was greater weight loss in the low carbohydrate ketogenic diet group than in the low fat diet group (5.8 kg versus 1.9 kg, $P=0.002$). Both of these studies support the findings presented in the present paper.

CONCLUSIONS

The data presented in the present study showed that a ketogenic diet acted as a natural therapy for weight reduction in obese patients. This is a unique study monitoring the effect of a ketogenic diet for 24 weeks. There was a significant decrease in the level of triglycerides, total cholesterol, LDL cholesterol and glucose, and a significant increase in the level of HDL cholesterol in the patients. The side effects of drugs commonly used for the reduction of body weight in such patients were not observed in patients who were on the ketogenic diet. Therefore, these results indicate that the administration of a ketogenic diet for a relatively long period of time is safe. Further studies elucidating the molecular mechanisms of a ketogenic diet are in progress in our laboratory. These studies will open new avenues into the potential therapeutic uses of a ketogenic diet and ketone bodies.

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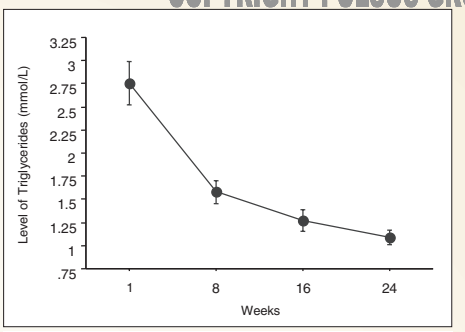

Figure 6) *Changes in the level of triglycerides in obese patients during treatment with a ketogenic diet over a period of 24 weeks. The values are expressed as mean ± SEM*

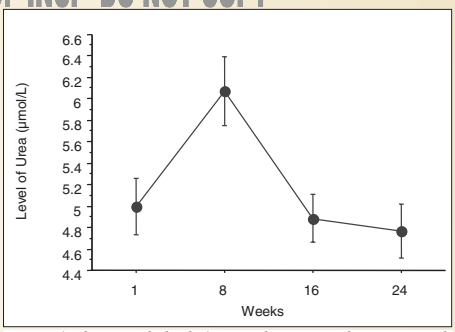

Figure 8) *Changes in the level of urea in obese patients during a 24-week ketogenic diet. The level of urea is expressed as mean ± SEM*

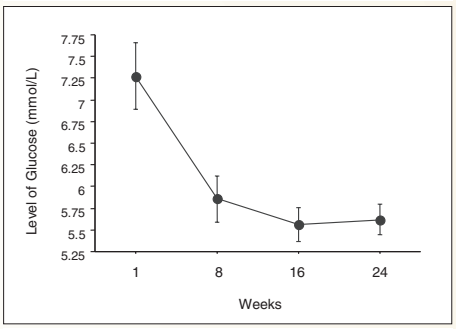

Figure 7) *Decreased levels of blood glucose (expressed as mean ± SEM) in obese patients at eight, 16 and 24 weeks during the administration of a ketogenic diet*

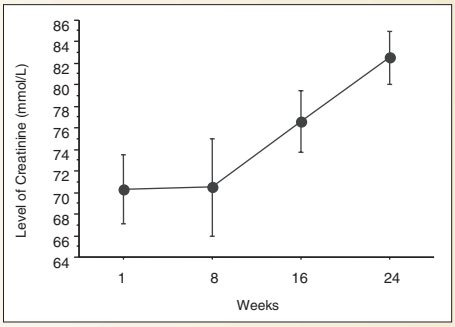

Figure 9) *Changes in the level of creatinine in obese patients during a 24-week ketogenic diet. Values are expressed as mean ± SEM*

syndrome and pyruvate dehydrogenase deficiency, which are both associated with cerebral energy failure and seizures (26).

One argument against the consumption of a high fat diet is that it causes obesity. The major concern in this regard is whether a high percentage of dietary fat promotes weight gain more than a low percentage of fat intake. Because fat has a higher caloric density than carbohydrate, it is thought that the consumption of a high fat diet will be accompanied by a higher energy intake (31). On the contrary, recent studies from our laboratory (12) and many other laboratories (24,32-34) have observed that a ketogenic diet can be used as a therapy for weight reduction in obese patients.

It has been found that a sugary diet is the root cause of various chronic diseases of the body. A recent study (35) showed that sugar can accelerate aging. Several recent studies (36,37) have pointed to the fact that a diet with a high glycemic load is independently associated with the development of cardiovascular diseases, type II diabetes and certain forms of cancer. Glycemic load refers to a diet of different foods that have a high glycemic index. Glycemic index is a measure of the elevation of glucose levels following the ingestion of a carbohydrate. The classification of a carbohydrate based on its glycemic index provided a better predictor of risk for coronary artery diseases than the traditional method of classification of carbohydrate into simple or complex forms (38). In other studies (38-46), it was shown that the risk of dietary glycemic load from refined carbohydrates was independent of other known risk factors for coronary diseases.

It is now evident that high carbohydrate diets increase fasting plasma triglyceride concentrations (47-51) and decrease HDL cholesterol concentrations (52-55). These changes are associated with enhanced atherogenesis (55). However, it has been shown that short-term ketogenic diets improve the lipid disorders that are characteristic of atherogenic dyslipidemia (56). It has also been found that sugary drinks decreased blood levels of vitamin E, thus reducing the amount of antioxidants in the body. It has been proven, beyond a doubt, that disrupting the oxidant-antioxidant status of the cell will lead to various diseases of the body (57).

The relation between a high fat diet and cancer is not conclusive. Recent epidemiological studies (17,58-60) could not explain a specific causal relationship between dietary fat and cancer. It has been found that altered energy metabolism and substrate requirements of tumour cells provide a target for

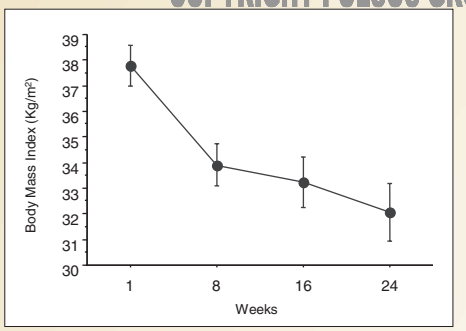

Figure 2) *Decrease in body mass index at eight, 16 and 24 weeks during the administration of a ketogenic diet in obese patients. The values are expressed as mean ± SEM*

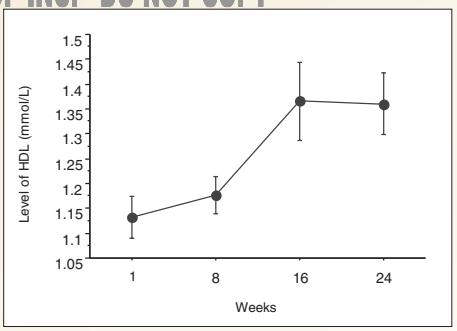

Figure 4) *Changes in the level of high density lipoprotein (HDL) cholesterol in obese patients during treatment with a ketogenic diet for a period of 24 weeks. Data are expressed as mean ± SEM*

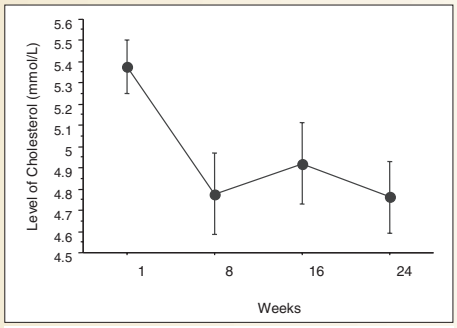

Figure 3) *Decreased levels of total cholesterol (expressed as mean ± SEM) in obese patients at eight, 16 and 24 weeks during the administration of a ketogenic diet*

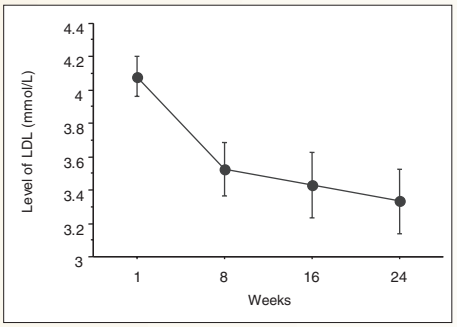

Figure 5) *Changes in the level of low density lipoprotein (LDL) cholesterol during treatment with a ketogenic diet in obese patients at eight, 16 and 24 weeks. The values are expressed as mean ± SEM*

The level of triglycerides decreased significantly after 24 weeks of treatment. The initial level of triglycerides was 2.75±0.23 mmol/L, whereas at week 24, the level decreased to 1.09±0.08 mmol/L (Figure 6). The level of blood glucose significantly decreased at week 24. The initial blood glucose level and its level at the eighth, 16th and 24th week were 7.26±0.38 mmol/L, 5.86±0.27 mmol/L, 5.56±0.19 mmol/L and 5.62±0.18 mmol/L, respectively (Figure 7). The changes in the levels of urea (Figure 8) and creatinine (Figure 9) were not statistically significant.

DISCUSSION

Until recently, ketosis was viewed with apprehension in the medical world; however, current advances in nutritional research have discounted this apprehension and increased public awareness about its favourable effects. In humans, ketone bodies are the only additional source of brain energy after glucose (23,24). Thus, the use of ketone bodies by the brain could be a significant evolutionary development that occurred in parallel with brain development in humans. Hepatic generation of ketone bodies during fasting is essential to provide an alternate fuel to glucose. This is necessary to spare the destruction of muscle from glucose synthesis.

A ketogenic diet is clinically and experimentally effective in antiepileptic and antiobesity treatments; however, the molecular mechanisms of its action remain to be elucidated. In some cases, a ketogenic diet is far better than modern anticonvulsants (25). Recently, it has been shown that a ketogenic diet is a safe potential alternative to other existing therapies for infantile spasms (27). It was further shown that a ketogenic diet could act as a mood stabilizer in bipolar illness (28). Beneficial changes in the brain energy profile have been observed in subjects who are on a ketogenic diet (28). This is a significant observation because cerebral hypometabolism is a characteristic feature of those who suffer from depression or mania (28). It has also been found that a ketogenic diet affects signal transduction in neurons by inducing changes in the basal status of protein phosphorylation (29). In another study (30), it was shown that a ketogenic diet induced gene expression in the brain. These studies provide evidence to explain the actions of a ketogenic diet in the brain.

One of the mechanisms of a ketogenic diet in epilepsy may be related to increased availability of beta-hydroxybutyrate, a ketone body readily transported through the blood-brain barrier. In support of this hypothesis, it was found that a ketogenic diet was the treatment of choice for glucose transporter protein

TABLE 1
Patient data at baseline before treatment with the ketogenic diet

	n	Age (years)	Height (m)	Weight (kg)	Body mass index (kg/m^2)
Men	39	42.6±1.7	1.7±0.01	102.4±3.7	35.9±1.2
Women	44	40.6±1.6	1.6±0.01	99.8±2.9	39.4±1.0

All data are mean ± SEM

TABLE 2
Composition of the capsule*

Para-aminobenzoic acid (PH)	30 mg
Vitamin B_1 (thiamin mononitrate) (BP)	15 mg
Vitamin B_2 (riboflavin) (BP)	3 mg
Vitamin B_5 (nicotinamide) (BP)	25 mg
Vitamin B_3 (calcium pantothenate) (PH)	3 mg
Vitamin B_6 (pyridoxine HCl) (BP)	5 mg
Vitamin B_{12} (cyanocobalamin) (BP)	10 µg
Biotin (PH)	5 µg
Folic acid (BP)	100 µg
Vitamin C (ascorbic acid) BP	60 mg
Vitamin A (retinol) (USP; 2000 IU)	0.6 mg
Vitamin D (calciferol) (INN; 200 IU)	5 µg
Vitamin E (tocopherol acetate) (USNF)	10 mg
Lecithin (PH)	40 mg
Wheat germ oil	100 mg
Lysine (FP)	40 mg
Methionine (DAB)	60 mg
Rutin (DAB) (rutoside) (INN)	10 mg
Iron (as fumarate; BP)	12 mg
Calcium (as dicalcium phosphate) (BP)	52 mg
Phosphorus (as dicalcium phosphate) (BP)	40 mg
Potassium (as KCl) (BP)	2 mg
Zinc (as $ZnSO_4$) (BP)	8 mg
Copper (as $CuSO_4$) (BP)	1 mg
Manganese (as $MnSO_4$) (BP)	2 mg
Iodine (as potassium iodide) (BP)	trace
Ginseng (Siberian) (5:1 concentrated extract)	4 mg

**Net weight 45 g. BP British Pharmacopoeia; DAB German Pharmacopoeia; FP French Pharmacopoeia; INN International nonpropietary names; IU International units; PH Swiss Pharmacopoeia; USNF United States National Formulary; USP United States Pharmacopoeia*

was to investigate the long-term effects of a ketogenic diet on obesity and obesity-associated risk factors in a large population of obese patients.

PATIENTS AND METHODS

Patients and biochemical analysis

The prospective study was carried out at the Academic Department of Surgery, Consultation and Training Centre, Faculty of Medicine, Kuwait University (Jabriya, Kuwait) in 83 obese subjects (39 men and 44 women). The body mass index (BMI) of men and women was 35.9±1.2 kg/m^2 and 39.4±1.0 kg/m^2, respectively. The mean age was 42.6±1.7 years and 40.6±1.6 years for men and women, respectively. The mean age, initial height, weight and BMI for all patients are given in Table 1. Fasting blood tests were carried out for all of the subjects. Initially, all patients were subjected to liver and renal function tests, and glucose and lipid profiles, using fasting blood samples, and a complete blood count. Thereafter, fasting blood samples were tested for total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, blood sugar, urea and creatinine levels at the eighth, 16th and 24th week. In addition, weight and height measurements, and blood pressure were monitored at each visit.

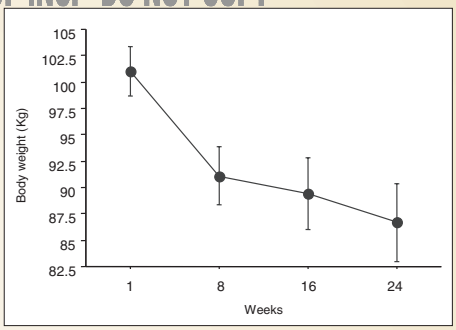

Figure 1) *Reduction in body weight at eight, 16 and 24 weeks following the administration of the ketogenic diet in obese patients. The weights are expressed as mean ± SEM*

Protocol for ketogenic diet-induced body weight reduction

All 83 subjects received the ketogenic diet consisting of 20 g to 30 g of carbohydrate in the form of green vegetables and salad, and 80 g to 100 g of protein in the form of meat, fish, fowl, eggs, shellfish and cheese. Polyunsaturated and monounsaturated fats were also included in the diet. Twelve weeks later, an additional 20 g of carbohydrate were added to the meal of the patients to total 40 g to 50 g of carbohydrate. Micronutrients (vitamins and minerals) were given to each subject in the form of one capsule per day (Table 2).

Statistical analysis

Statistical differences between body weight, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, level of fasting blood sugar, and urea and creatinine levels before and after the administration of the ketogenic diet were analyzed using a paired Student's *t* test using the Stat-view version 4.02 (Abacus Concepts Inc, USA). Weight, BMI and all biochemical parameters are expressed as mean ± SEM.

RESULTS

The mean initial weight of the subjects was 101.03±2.33 kg. The weight decreased significantly during all stages of the treatment period. The body weights at the eighth, 16th and 24th week were 91.10±2.76 kg, 89.39±3.4 kg and 86.67±3.70 kg, respectively (Figure 1). Similar to the loss in body weight, a significant decrease was observed in the BMI of the patients following the administration of the ketogenic diet. The initial BMI, and the BMI after the eighth, 16th and 24th week were 37.77±0.79 kg/m^2, 33.90±0.83 kg/m^2, 33.24±1.00 kg/m^2 and 32.06±1.13 kg/m^2, respectively (Figure 2).

The level of total cholesterol showed a significant decrease from week 1 to week 24 (Figure 3). The level of HDL cholesterol significantly increased (Figure 4), whereas LDL cholesterol levels significantly decreased with treatment (Figure 5).

البحث الثاني

CLINICAL CARDIOLOGY

Long-term effects of a ketogenic diet in obese patients

Hussein M Dashti MD PhD FICS FACS[1], Thazhumpal C Mathew MSc PhD FRCPath[4], Talib Hussein MB ChB[5], Sami K Asfar MB ChB MD FRCSEd FACS[1], Abdulla Behbahani MB ChB FRCS FACSI PhD FICS FACS[1], Mousa A Khoursheed MB ChB FRCS FICS[1], Hilal M Al-Sayer MD PhD FICS FACS[1], Yousef Y Bo-Abbas MD FRCPC[2], Naji S Al-Zaid BSc PhD[3]

HM Dashti, TC Mathew, T Hussein, et al. Long-term effects of a ketogenic diet in obese patients. Exp Clin Cardiol 2004;9(3):200-205.

BACKGROUND: Although various studies have examined the short-term effects of a ketogenic diet in reducing weight in obese patients, its long-term effects on various physical and biochemical parameters are not known.

OBJECTIVE: To determine the effects of a 24-week ketogenic diet (consisting of 30 g carbohydrate, 1 g/kg body weight protein, 20% saturated fat, and 80% polyunsaturated and monounsaturated fat) in obese patients.

PATIENTS AND METHODS: In the present study, 83 obese patients (39 men and 44 women) with a body mass index greater than 35 kg/m^2, and high glucose and cholesterol levels were selected. The body weight, body mass index, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, fasting blood sugar, urea and creatinine levels were determined before and after the administration of the ketogenic diet. Changes in these parameters were monitored after eight, 16 and 24 weeks of treatment.

RESULTS: The weight and body mass index of the patients decreased significantly (P<0.0001). The level of total cholesterol decreased from week 1 to week 24. HDL cholesterol levels significantly increased, whereas LDL cholesterol levels significantly decreased after treatment. The level of triglycerides decreased significantly following 24 weeks of treatment. The level of blood glucose significantly decreased. The changes in the level of urea and creatinine were not statistically significant.

CONCLUSIONS: The present study shows the beneficial effects of a long-term ketogenic diet. It significantly reduced the body weight and body mass index of the patients. Furthermore, it decreased the level of triglycerides, LDL cholesterol and blood glucose, and increased the level of HDL cholesterol. Administering a ketogenic diet for a relatively longer period of time did not produce any significant side effects in the patients. Therefore, the present study confirms that it is safe to use a ketogenic diet for a longer period of time than previously demonstrated.

Key Words: *Diet; Ketosis; Obesity*

Obesity has become a serious chronic disease in both developing and developed countries. Furthermore, it is associated with a variety of chronic diseases (1-4). It is estimated that in the United States alone approximately 300,000 people die each year from obesity-related diseases (5,6). Different methods for reducing weight using reduced calorie and fat intake combined with exercise have failed to show sustained long-term effects (7-9). Recent studies from various laboratories (10,11), including our own (12), have shown that a high fat diet rich in polyunsaturated fatty acids (ketogenic diet) is quite effective in reducing body weight and the risk factors for various chronic diseases. The ketogenic diet was originally introduced in 1920 (13). In this diet, the fat to carbohydrate ratio is 5:1. While there was a significant decrease in the weight of obese patients who were on a ketogenic diet (12), the reverse occurred when the diet changed to one high in carbohydrates (14).

It should be noted that the concept that fat can be eaten ad libitum and still induce weight loss in obese subjects is not a recent one (13-33). Ketosis occurs as a result of the change in the body's fuel from carbohydrate to fat. Incomplete oxidation of fatty acids by the liver results in the accumulation of ketone bodies in the body. A ketogenic diet maintains the body in a state of ketosis, which is characterized by an elevation of D-b-hydroxybutyrate and acetoacetate.

Mild ketosis is a natural phenomenon that occurs in humans during fasting and lactation (19,20). Postexercise ketosis is a well-known phenomenon in mammals. Although most of the changes in the physiological parameters induced following exercise revert back to their normal values rapidly, the level of circulating ketone bodies increases for a few hours after muscular activity ceases (21). It has been found that in trained individuals, a low blood ketone level protects against the development of hypoglycemia during prolonged intermittent exercise (22). In addition, ketosis has a significant influence on suppressing hunger. Thus, a ketogenic diet is a good regulator of the body's calorie intake and mimics the effect of starvation in the body.

It is generally believed that high fat diets may lead to the development of obesity and several other diseases such as coronary artery disease, diabetes and cancer. This view, however, is based on studies carried out in animals that were given a high fat diet rich in polyunsaturated fatty acids. In contrast, our laboratory has recently shown that a ketogenic diet modified the risk factors for heart disease in obese patients (12).

Although various short-term studies examining the effect of a ketogenic diet in reducing the weight of obese patients have been carried out (10), its long-term effects in obese subjects are not known (15). Therefore, the purpose of the present study

Departments of [1]Surgery, [2]Medicine and [3]Physiology, Faculty of Medicine, and [4]Faculty of Allied Health Sciences, Kuwait University, Safat; [5]Ministry of Health, Safat, Kuwait
Correspondence: Dr Naji Al-Zaid, Department of Physiology, Faculty of Medicine, PO Box 24923, 13110, Safat, Kuwait. Telephone 965-531-9593, fax 965-531-9597, e-mail alzaidnajeee@hotmail.com

TABLE I.

CHANGES IN THE LEVEL OF VARIOUS PHYSICAL AND BIOCHEMICAL PARAMETERS AT THE END OF THE TREATMENT PERIOD (WEEK 12)

Physical and biochemical parameters	Week 1*	Week 12*	*P*
Weight (kg)	99.2 ± 2.1	85.9 ± 2.6	<0.0001
Body mass index	37.4 ± 0.7	33.0 ± 0.8	<0.0001
Cholesterol (mM/L)	5.4 ± 0.1	4.9 ± 0.1	0.0022
HDL (mM/L)	1.2 ± 0.04	1.3 ± 0.04	0.0022
LDL (mM/L)	4.0 ± 0.1	3.5 ± 0.1	0.0160
Triacylglycerols (mM/L)	2.4 ± 0.2	1.2 ± 0.01	<0.0001
Glucose (mM/L)	7.0 ± 0.3	5.4 ± 0.1	0.0009

* Data are expressed as mean ± standard error.
HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol

increase fasting plasma triacylglycerol concentration[4] and decrease HDL cholesterol concentrations.[5]

The data presented in this study showed that a ketogenic diet, in addition to acting as a natural therapy for weight reduction in obese patients, significantly decreases the level of triacylglycerols, total cholesterol, LDL cholesterol, and glucose and increases the level of HDL. These results, therefore, indicate that the administration of a ketogenic diet for a relatively long period is safe and favorably modifies the risk factors of heart disease in obese patients.

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البحث الأول

PRELIMINARY REPORT

Ketogenic Diet Modifies the Risk Factors of Heart Disease in Obese Patients

Hussein M. Dashti, MD, PhD, FICS, FACS, Yousef Y. Bo-Abbas, MD, FRCPC,
Sami K. Asfar, MB ChB, MD, FRCS Ed, FACS,
Thazhumpal C. Mathew, MSc, PhD, FRCPath, Talib Hussein, MB ChB,
Abdulla Behbahani, MB ChB, FRCS, FACSI, PhD, FICS, FACS,
Mousa A. Khoursheed, MB ChB, FRCS, FICS, Hilal M. Al-Sayer, MD, PhD, FICS, FACS,
and Naji S. Al-Zaid, BSc, PhD

From the Department of Surgery, the Department of Medicine, and the Department of Physiology, Faculty of Medicine, the Department of MLS, Faculty of Allied Health, Kuwait University, Safat, Kuwait; and the Ministry of Health, Safat, Kuwait

INTRODUCTION

It is generally believed that high-fat diets may lead to the development of obesity and several other diseases such as coronary heart disease, diabetes, and cancer. This view is based on studies carried out in animals that were given a high-fat diet rich in polyunsaturated fatty acids. However, various recent epidemiologic studies have not explained a specific causal relation between dietary fat and obesity or obesity-associated diseases.[1]

Further, contrary to the common notion, a high intake of carbohydrates was found to increase the levels of triacylglycerols, total cholesterol, and low-density lipoprotein (LDL) cholesterol and decrease the level of high-density lipoprotein (HDL) cholesterol. Elevated levels of triacylglycerols and low levels of HDL were associated with hyperinsulinemia. Also, an elevated triacylglycerol level, particularly a high ratio of triacylglycerols to HDL, is an important predictor of heart attack.[2]

Recent studies have quite evidently shown that the ketogenic diet is a natural therapy for obesity and obesity-associated diseases. However, there are very few studies that have addressed the long-term influence of a ketogenic diet in modifying various obesity-associated diseases. Hence, the purpose of this study was to investigate the long-term effect of a ketogenic diet on the activation and modification of heart disease risk factors in obese patients.

MATERIALS AND METHODS

A prospective study was carried out at the Academic Department of Surgery, Consultation and Training Center, Faculty of Medicine, Kuwait University in 102 (42 male and 60 female) obese subjects whose body mass index was 37.4 ± 0.7. Mean age was 40.8 ± 1.0 y (58.8% female and 41.2% male). Fasting blood tests were carried out for all the subjects. Initially all the patients were subjected to liver and renal function tests. Their glucose and lipid profiles from fasting blood samples and complete blood count were performed. Thereafter, their fasting blood samples were tested for total cholesterol, HDL cholesterol, LDL cholesterol, triacylglycerol, and blood sugar at 4, 8, and 12 wk.

All 102 subjects received a ketogenic diet consisting of 20 to 30 g of carbohydrate in the form of green vegetables and salad and 80 to 100 g of proteins in the form of meat, fish, fowl, eggs, shellfish, and cheese. Polyunsaturated and monounsaturated fats were included in the diet. Twelve weeks later, an additional 20 g of carbohydrate was added to the meal, for a total of 50 g of carbohydrate. Micronutrients (vitamins and minerals) in the form of 1 capsule/d were given to each subject.

Statistical differences between various parameters before and after the administration of the ketogenic diet were analyzed by paired Student's *t* test with Statview 4.02. Weight, body mass index, and all biochemical parameters are expressed as mean ± standard error.

RESULTS

The changes in the level of the various physical and biochemical parameters examined are shown in Table I. The level of triacylglycerols showed a significant decrease from before treatment to 12 wk after treatment. The initial level of triacylglycerol was 2.4 mM/L ± 0.2; at 12 wk the level decreased to 1.2 mM/L ± 0.1. The level of total cholesterol decreased from week 1 to week 12. HDL cholesterol increased significantly, whereas LDL cholesterol decreased significantly.

The changes in various other physical and biochemical parameters observed before and after the treatment period with the corresponding *P* values are given in Table I. There was a significant reduction in body weight. The level of fasting blood sugar decreased significantly. In conclusion, consuming a ketogenic diet for 12 wk is safe, and it favorably modified the risk factors of heart disease in obese patients.

DISCUSSION

One argument against the consumption of a high-fat diet is that it causes obesity. Because fat has a caloric density higher than that of carbohydrate, it is thought that consumption of a high-fat diet will be accompanied by a higher energy intake. On the contrary, recent studies including those from our laboratory have confirmed that the ketogenic diet is a natural therapy for obesity.

In contrast, several current studies have pointed to the fact that a diet with a high glycemic load is independently associated with developing cardiovascular diseases, type 2 diabetes, and certain form of cancers.[1] Another study carried out in the United States showed that the risk of dietary glycemic load from refined carbohydrates is independent of other known risk factors of coronary diseases.[3] Now it is quite evident that high-carbohydrate diets

Correspondence to: Hussein M. Dashti, Department of Surgery, Faculty of Medicine, PO Box 24923, 13110 Safat, Kuwait. E-mail: thazhumpal@kuc01.kuniv.edu.kw

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اللهم إني أعتذر إليك من مظلوم ظُلِمَ بحضرتي فلم أنصره، ومن معروف أُسْدِيَ إلي فلم أشكره، ومن مسيءٍ اعتذر إليّ فلم أعذره، ومن ذي فاقة سألني فلم أُؤثره، ومن حق ذي حق لزمني لمؤمن فلم أوفره، ومن عيب مؤمن ظهر لي فلم أستره، ومن كل إثم عرض لي فلم أهجره، أعتذر إليك يا إلهي منهن ومن نظائرهن اعتذار ندامة يكون واعظاً لما بين يدي من أشباههن، فصلّ على محمد وآله واجعل ندامتي على ما وقعت فيه من الزلات وعزمي على ترك ما يعرض لي من السيئات توبة توجب لي محبتك يا محب التوّابين.

الإمام علي بن الحسين
زين العابدين (ع)

الروح باقية على العشرين