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International Journal of Obesity advance online publication 18 August 2009; doi: 10.1038/ijo.2009.149

Antiobesity and antidiabetic effects of biotransformed blueberry juice in KKAy mice

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ESSENCE OF ARTICLE

‘This study shows that BJ decreases hyperglycemia in diabetic mice, at least in part by reversing adiponectin levels. BJ also protects young pre-diabetic mice from developing obesity and diabetes. Thus, BJ may represent a novel complementary therapy and a source of novel therapeutic agents against diabetes mellitus”

ARTICLE

Abstract

Aim:

Biotransformation of blueberry juice by the Serratia vaccinii bacterium gave rise to adenosine monophosphate-activated protein kinase (AMPK) phosphorylation and glucose uptake in muscle cells and adipocytes, but inhibited adipogenesis. This study investigated the antiobesity and antidiabetic potential of biotransformed blueberry juice (BJ) in KKAy mice, rodent model of leptin resistance.

Methods:

BJ was incorporated in drinking water of KKAy mice. Parameters of body weight, food intake, plasma glucose, insulin, leptin, and adiponectin were measured. Before and after therapy, animals were subjected to an oral glucose tolerance test. At the end of treatment, liver, muscle, kidney, epididymal fat pad, abdominal fat pad, and dorsal fat pad were collected and weighed.

Results:

Incorporating BJ in drinking water protected young KKAy mice from hyperphagia and significantly reduced their weight gain. Moreover, BJ protected young KKAy mice against the development of glucose intolerance and diabetes mellitus. Chronic BJ administration in obese and diabetic KKAy mice reduced food intake and body weight. This effect could not fully explain the associated antidiabetic effect because BJ-treated mice still showed lower blood glucose level when compared with pair-fed controls. The adipokines pathway also seems to be involved because BJ significantly increased adiponectin levels in obese mice.

Conclusions:

This study shows that BJ decreases hyperglycemia in diabetic mice, at least in part by reversing adiponectin levels. BJ also protects young pre-diabetic mice from developing obesity and diabetes. Thus, BJ may represent a novel complementary therapy and a source of novel therapeutic agents against diabetes mellitus.

Keywords:

antiobesity, antidiabetic, adiponectin, KKAy mice, blueberry

Research Project: CHEMISTRY OF NATURAL PRODUCTS FOR PEST MANAGEMENT AND CROP DEVELOPMENT

Location: Natural Products Utilization Research

Resveratrol, Pterostilbene and Piceatannol in Vaccinium Berries

Authors ; Rimando, Agnes

Kalt, Wilhelmina - AGRICULTURE & AGRI-FOOD

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Submitted to: Journal of Agricultural and Food Chemistry

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Publication Date: July 3, 2004

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ESSENCE OF ARTICLE

"A study was done to determine the presence of resveratrol, pterostilbene and piceatannol in Vaccinium berries. …." These naturally occurring compounds known to be strong antioxidants and to have cancer chemopreventive activity will add to purported health benefits derived from consumption of these small fruits."

ARTICLE

Interpretive Summary: A study was done to determine the presence of resveratrol, pterostilbene and piceatannol in Vaccinium berries. Samples representing selections and cultivars of ten species from Mississippi, North Carolina,

Oregon, and Canada were analyzed by gas chromatography/mass spectrometry. Resveratrol was found in varying amounts between 7 and 5800 ng/g dry sample in bilberry, cranberry, deerberry, Elliott's blueberry, highbush blueberry, lingonberry, lowbush blueberry, rabbiteye blueberry, sparkleberry, and Partridgeberry. Lingonberry was found to have the highest content comparable to that found in grapes, 6500 ng/g dry sample. Pterostilbene was found in rabbiteye blueberry and deerberry at levels 99-520 ng/g dry sample. Piceatannol was found in deerberry and highbush blueberry at levels 138 ' 422 ng/g dry sample. These naturally occurring compounds known to be strong antioxidants and to have cancer chemopreventive activity will add to purported health benefits derived from consumption of these small fruits.

Technical Abstract: A study was conducted to determine the presence of resveratrol, pterostilbene and piceatannol in Vaccinium berries. Samples representing selections and cultivars of ten species from Mississippi, North Carolina, Oregon, and Canada were analyzed by gas chromatography/mass spectrometry. Resveratrol was found in V. angustifolium (lowbush blueberry), V. arboretum (sparkleberry), V. ashei (rabbiteye blueberry), V. corymbosum (highbush blueberry), V. elliottii (Elliott's blueberry), V. macrocarpon (cranberry), V. myrtillus (bilberry), V. stamineum (deerberry), V. vitis-ideae var. vitis-ideae (lingonberry), and V. vitis-ideae var. minor (Partridgeberry) at levels between 7 and 5800 ng/g dry sample. Lingonberry was found to have the highest content, 5800 ng/g dry sample, comparable to that found in grapes, 6500 ng/g dry sample. Pterostilbene was found in two cultivars of V. ashei and in V. stamineum at levels 99-520 ng/g dry sample. Piceatannol was found in V. corymbosum and V. stamineum at levels 138 ' 422 ng/g dry sample. These naturally occurring stilbenes, known to be strong antioxidants and to have cancer chemopreventive activity, will add to purported health benefits derived from consumption of these small fruits.

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Science Express Index

Reports

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Accepted on April 23, 2009

Inhibition of Hedgehog Signaling Enhances Delivery of Chemotherapy in a Mouse Model of Pancreatic Cancer

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ESSENCE OF ARTICLE

" We tested whether the delivery and efficacy of gemcitabine in the mice could be improved by coadministration of IPI-926, a drug that depletes tumor-associated stromal tissue by inhibiting the Hedgehog cellular signaling pathway. The combination therapy produced a transient increase in intratumoral vascular density and intratumoral concentration of gemcitabine, leading to transient stabilization of disease. Thus, inefficient drug delivery may be an important contributor to chemoresistance in pancreatic cancer."

ARTICLE

Pancreatic ductal adenocarcinoma (PDA) is among the most lethal human cancers, in part because it is insensitive to many chemotherapeutic drugs. Studying a mouse model of PDA that is refractory to the clinically used drug gemcitabine, we found that the tumors in this model were poorly perfused and poorly vascularized, properties that are shared with human PDA. We tested whether the delivery and efficacy of gemcitabine in the mice could be improved by coadministration of IPI-926, a drug that depletes tumor-associated stromal tissue by inhibiting the Hedgehog cellular signaling pathway. The combination therapy produced a transient increase in intratumoral vascular density and intratumoral concentration of gemcitabine, leading to transient stabilization of disease. Thus, inefficient drug delivery may be an important contributor to chemoresistance in pancreatic cancer.

PERSPECTIVES

Cancer

Breaching the Cancer Fortress

Peter Olson and Douglas Hanahan (12 June 2009)

Science 324 (5933), 1400. [DOI: 10.1126/science.1175940]

| Summary » | Full Text » | PDF »

In Science Signaling

EDITORS' CHOICE

Cancer

It's All in the Delivery

Paula A. Kiberstis (16 June 2009)

Sci. Signal. 2 (75), ec202. [DOI: 10.1126/scisignal.275ec202]

| Abstract »

THIS ARTICLE HAS BEEN CITED BY OTHER ARTICLES:

Following the Hedgehog to New Cancer Therapies.

A. A. Dlugosz and M. Talpaz (2009)

N. Engl. J. Med.

| Full Text » | PDF »

Breaching the Cancer Fortress.

P. Olson and D. Hanahan (2009)

Science 324, 1400-1401

| Abstract » | Full Text » | PDF »

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http://info.cancerresearchuk.org/news/archive/pressreleases/2009/may/Scientists-shed-new-light

THURSDAY 21 MAY 2009

Cancer Research UK Press Release

CANCER RESEARCH UK scientists led an international team of investigators who have discovered a new mechanism that may explain why pancreatic cancer patients are often resistant to a common chemotherapy treatment called gemcitabine*, according to a study published in Science** today (Thursday).

It is hoped this study will help scientists overcome a common resistance to gemcitabine and make future chemotherapy drugs more effective.

Pancreatic cancer is diagnosed in 230,000 people across the world***, with 7,600 new cases in the UK and 37,000 new cases in the United States each year. Only three per cent of patients survive for five years or more.

The scientists at Cancer Research UK's Cambridge Research Institute - who were co-funded by The Lustgarten Foundation and the National Institutes of Health, sought to understand why promising drugs generally fail in pancreatic cancer clinical trials. They found that a genetically modified mouse model of pancreatic cancer that closely resembles human cancer was also largely resistant to gemcitabine treatment.

The scientists found in these mouse studies that pancreatic cancer is resistant to chemotherapy because the tumours tend to have poor networks of blood vessels called vasculature, which makes it harder for drugs to reach the tumour.

Working with groups at Addenbrooke's Hospital, the Johns Hopkins Hospital, the MD Anderson Cancer Centre, University of Pittsburghand the Fred Hutchison Cancer Research Centre, the group also noted that human pancreatic cancer samples also contained a deficient blood supply, suggesting that their observation should also be applicable to patients.

Senior author Dr David Tuveson, group leader in tumour modeling and experimental medicine at Cancer Research UK's Cambridge Research Institute, said: "We're extremely excited by these results as they may help explain the disappointing response that many pancreatic cancer patients receive from chemotherapy drugs."

The study also found that the genetically modified mice displayed the same resistance to gemcitabine as seen in human pancreatic cancer, whereas the transplantation mouse models traditionally used to develop chemotherapy treatments were sensitive to gemcitabine. This means that the new genetically modified models could prove superior in developing new treatments in the future.

When the scientists used a new compound called IPI-926****, which was created by Infinity Pharmaceuticals, in combination with gemcitabine in the genetically modified animals, they noticed increased cell death and a reduction of the pancreatic tumour size. They believe that using this combination may also re-open the door to several new treatments which have, so far, proven disappointing in patient trials for pancreatic cancer because of poor drug delivery.

"But these are early days and we need to show this approach is safe to use in humans before we can consider adding the new compound to cancer treatments," said Dr Tuveson.

These findings may also help to explain why pancreatic cancer does not respond to anti-angiogenic drugs such as VEGF inhibitors when many other cancers do. These are a new class of drugs which starve the tumour by restricting its blood supply. As pancreatic cancers don't seem to need as good a supply of blood to the tumour as other cancers, the scientists believe that they may need to introduce additional drugs to help stop tumour growth.

Kerri Kaplan, executive director of The Lustgarten Foundation, the largest private funder of pancreatic cancer research in the United States, said: "Because pancreatic cancer is so difficult to treat with standard chemotherapy, these study results demonstrate progress toward greater understanding of how to treat this swift, silent and deadly disease. The Foundation remains committed to supporting research that improves our understanding of pancreatic cancer, in the hope that one day, early diagnostic tools and new, improved treatments can be found."

Dr Lesley Walker, Cancer Research UK's director of cancer information said: "This is a very substantial finding. If these results hold in future studies, we hope that scientists will be able to make better use of current treatments and develop a range of new options which will help people with pancreatic cancer live longer.

"Cancer Research UK's five year strategy highlights the importance of targeting areas of unmet medical need, such as pancreatic cancer, so we can have the greatest impact on reducing cancer deaths in the future. Results like these give us real confidence that we will combine this focus with our other research efforts and meet our goals of improving survival from all forms of the disease."

ENDS

For media enquiries, please contact the Cancer Research UK press office on 020 7061 8311 or, out of hours, the duty press officer on 07050 264 059.

Notes to editors:

Listen to an interview with Dr Tuveson, the senior author on the study

*This study used gemcitabine (Gemzar) which is one of a group of chemotherapy drugs called anti-metabolites. Anti-metabolites are similar to normal body molecules but they are slightly different in structure. These differences mean that anti-metabolites stop cells making DNA. Cancer cells need DNA to multiply. You can find out more about this drug and other treatments for pancreatic cancer on Cancer Research UK’s patient information website CancerHelp UK

**Inhibition of Hedgehog Signalling Enhances Delivery of Chemotherapy in a Mouse Model of Pancreatic Cancer. Science. May 2009. Kenneth P. Olive et al.

***Estimates show 230,000 people across the world were diagnosed with pancreatic cancer in 2002.

****IPI-926 is novel, selective, potent, small molecule Hh pathway inhibitor that directly blocks the activity of Smoothened (Smo). It is currently being investigated in a Phase 1 clinical trial by Infinity Pharmaceuticals. Because Smo plays a critical role in the malignant activation of the Hh pathway, Smo may be a target for the management of a broad range of cancers.

About pancreatic cancer

Around 20 people every day are diagnosed with pancreatic cancer in the UK and it is the fifth most common cause of cancer death. For more UK pancreatic statistics go to Cancer Research UK’s here

Pancreatic cancer is the fourth leading cause of cancer death in the US according to the American Cancer Society in 2008 an estimated 37,000 people were diagnosed with pancreatic cancer and about 34,000 died of the disease.

About the Hedgehog Signaling Pathway

Malignant activation of the Hedgehog signalling pathway is implicated in multiple cancer settings. In certain cancers, the Hedgehog ligand derived from the tumour either signals to the surrounding stroma, such as in pancreatic cancer, or to a subpopulation of Hedgehog-dependent chemo-resistant progenitor cells, as may be found in small cell lung cancer (SCLC), chronic myelogenous leukemia, and multiple myeloma.

These cancers, therefore, may be classified as Hedgehog ligand-dependent. In certain other cancers, there is a genetic mutation resulting in activation of the pathway. These cancers thereby function independently of the Hedgehog ligand and include medulloblastoma and basal cell carcinoma.

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http://www.jewishhospitalcincinnati.com/cholesterol/Research/Low_serum_levels.html

Low serum 25 (OH) vitamin D levels (,32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients

WAQAS AHMED, NASEER KHAN, CHARLES J. GLUECK, SUMAN PANDEY, PING WANG, NAILA GOLDENBERG, MUHAMMAD UPPAL, and SURAJ KHANAL

CINCINNATI, OHIO

(Translational Research 2009;153:11–16)

Overall Summary:

ESSENCE OF ARTICLE

“Many patients cannot tolerate statin medications because they develop muscle cramps, pain, and weakness, and sometimes the muscles are tender to touch. We have found that most of these patients are deficient in serum Vitamin D. It appears that Vitamin D deficiency can produce mild muscle injury, and when this is superimposed on mild muscle injury associated with statin medications, then there is a synergistic effect, and the muscles hurt enough (myositis) so that the patients stop life-protecting statin medications. In patients who had statin intolerance because of myositis, and who had concurrent low serum Vitamin D, we reversed the vitamin D deficiency with 50,000 units of Vitamin D once per week or 2000 units per day, and when we restarted the statins, the great majority of patients tolerated them well, without myositis.”

ARTICLE

Many patients cannot tolerate statin medications because they develop muscle cramps, pain, and weakness, and sometimes the muscles are tender to touch. We have found that most of these patients are deficient in serum Vitamin D. It appears that Vitamin D deficiency can produce mild muscle injury, and when this is superimposed on mild muscle injury associated with statin medications, then there is a synergistic effect, and the muscles hurt enough (myositis) so that the patients stop life-protecting statin medications. In patients who had statin intolerance because of myositis, and who had concurrent low serum Vitamin D, we reversed the vitamin D deficiency with 50,000 units of Vitamin D once per week or 2000 units per day, and when we restarted the statins, the great majority of patients tolerated them well, without myositis.

Scientific Summary

Our specific aims were to determine whether low serum 25 (OH) vitamin D (D2 1 D3) (,32 ng/mL) was associated with myalgia in statin-treated patients and whether the myalgia could be reversed by vitamin D supplementation while continuing statins.

After excluding subjects who took corticosteroids or supplemental vitamin D, serum 25 (OH) D was measured in 621 statin-treated patients, which consisted of 128 patients with myalgia at entry and 493 asymptomatic patients. The 128 myalgic patients had lower mean 6 standard deviation (SD) serum vitamin D than the 493 asymptomatic patients (28.6 6 13.2 vs 34.2 6 13.8 ng/mL, P , 0.0001), but they did not differ (p . 0.05) by age, body mass index (BMI), type 2 diabetes, or creatine kinase levels.

By analysis of variance, which was adjusted for race, sex, and age, the least square mean (6 standard error [SE]) serum vitamin D was lower in the 128 patients with myalgia than in the 493 asymptomatic patients (28.7 6 1.2 vs 34.3 6 0.6 ng/mL, P , 0.0001). Serum 25 (OH) D was low in 82 of 128 (64%) patients with myalgia versus 214 of 493 (43%) asymptomatic patients (c2 5 17.4, P , 0.0001). Of the 82 vitamin-

D–deficient, myalgic patients, while continuing statins, 38 were given vitamin D (50,000 units/week for 12 weeks), with a resultant increase in serum vitamin D from 20.4 6 7.3 to 48.2 6 17.9 ng/mL (P , 0.0001) and resolution of myalgia in 35 (92%).

We speculate that symptomatic myalgia in statin-treated patients with concurrent vitamin D deficiency may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle.

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http://www3.interscience.wiley.com/journal/122380530/abstract

International Journal of Cancer

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Cancer Cell Biology

E2F4 and ribonucleotide reductase mediate S-phase arrest in colon cancer cells treated with chlorophyllin

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KEYWORDS

colorectal cancer • chlorophyllin • ribonucleotide reductase • Rb/E2F pathway

ESSENCE OF ARTICLE

“Chlorophyllin (CHL) is a water-soluble derivative of chlorophyll that exhibits cancer chemopreventive properties, but which also has been studied for its possible cancer therapeutic effects.”

ARTICLE

ABSTRACT

Chlorophyllin (CHL) is a water-soluble derivative of chlorophyll that exhibits cancer chemopreventive properties, but which also has been studied for its possible cancer therapeutic effects. We report here that human colon cancer cells treated with CHL accumulate in S-phase of the cell cycle, and this is associated with reduced expression levels of p53, p21, and other G1/S checkpoint controls. At the same time, E2F1 and E2F4 transcription factors become elevated and exhibit increased DNA binding activity. In CHL-treated colon cancer cells, bromodeoxyuridine pulse-chase experiments provided evidence for the inhibition of DNA synthesis. Ribonucleotide reductase (RR), a pivotal enzyme for DNA synthesis and repair, was reduced at the mRNA and protein level after CHL treatment, and the enzymatic activity was inhibited in a concentration-dependent manner both in vitro and in vivo. Immunoblotting revealed that expression levels of RR subunits R1, R2, and p53R2 were reduced by CHL treatment in HCT116 (p53+/+) and HCT116 (p53-/-) cells, supporting a p53-independent mechanism. Prior studies have shown that reduced levels of RR small subunits can increase the sensitivity of colon cancer cells to clinically used DNA-damaging agents and RR inhibitors. We conclude that by inhibiting R1, R2, and p53R2, CHL has the potential to be effective in the clinical setting, when used alone or in combination with currently available cancer therapeutic agents.

Received: 23 March 2009; Accepted: 30 April 2009

DIGITAL OBJECT IDENTIFIER (DOI)

10.1002/ijc.24559 About DOI or MEDLINE]

Diabetologia. 2007 Sep;50(9):1795-807. Epub 2007 Jun 22. Links

A Palaeolithic diet improves glucose tolerance more than a Mediterranean-like diet in individuals with ischaemic heart disease.

Lindeberg S, Jönsson T, Granfeldt Y, Borgstrand E, Soffman J, Sjöström K, Ahrén B.

Department of Medicine, Hs 32, University of Lund, SE-221 85, Lund, Sweden. staffan.lindeberg@med.lu.se

ESSENCE OF ARTICLE

CONCLUSIONS/INTERPRETATION: “A Palaeolithic diet may improve glucose tolerance independently of decreased waist circumference.”

ARTICLE

AIMS/HYPOTHESIS: Most studies of diet in glucose intolerance and type 2 diabetes have focused on intakes of fat, carbohydrate, fibre, fruits and vegetables. Instead, we aimed to compare diets that were available during human evolution with more recently introduced ones. METHODS: Twenty-nine patients with ischaemic heart disease plus either glucose intolerance or type 2 diabetes were randomised to receive (1) a Palaeolithic ('Old Stone Age') diet (n = 14), based on lean meat, fish, fruits, vegetables, root vegetables, eggs and nuts; or (2) a Consensus (Mediterranean-like) diet (n = 15), based on whole grains, low-fat dairy products, vegetables, fruits, fish, oils and margarines. Primary outcome variables were changes in weight, waist circumference and plasma glucose AUC

(AUC Glucose(0-120)) and plasma insulin AUC (AUC Insulin(0-120)) in OGTTs. RESULTS: Over 12 weeks, there was a 26% decrease of AUC Glucose(0-120) (p = 0.0001) in the Palaeolithic group and a 7% decrease (p = 0.08) in the Consensus group. The larger (p = 0.001) improvement in the Palaeolithic group was independent (p = 0.0008) of change in waist circumference (-5.6 cm in the Palaeolithic group, -2.9 cm in the Consensus group; p = 0.03). In the study population as a whole, there was no relationship between change in AUC Glucose(0-120) and changes in weight (r = -0.06, p = 0.9) or waist circumference (r = 0.01, p = 1.0). There was a tendency for a larger decrease of AUC Insulin(0-120) in the Palaeolithic group, but because of the strong association between change in AUC Insulin(0-120) and change in waist circumference (r = 0.64, p = 0.0003), this did not remain after multivariate analysis. CONCLUSIONS/INTERPRETATION: A Palaeolithic diet may improve glucose tolerance independently of decreased waist circumference.

PMID: 17583796 [PubMed - indexed for MEDLINE]

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http://www.staffanlindeberg.com/DiabetesStudy.html

The original human diet is good for people with diabetes

Lindeberg, S, Jönsson, T, Granfeldt, Y, Borgstrand, E, Soffman, J, Sjöström, K, and Ahrén, B. A Palaeolithic diet improves glucose tolerance more than a Mediterranean-like diet in individuals with ischaemic heart disease. Diabetologia, 2007; In press: http://www.springerlink.com/content/h7628r66r0552222

ESSENCE OF ARTICLE

"If you want to prevent or treat diabetes type 2, it may be more efficient to avoid some of our modern foods than to count calories or carbohydrate >>."

ARTICLE

In a clinical study, we compared 14 patients who were advised to consume an 'ancient' (Paleolithic, 'Old stone Age') diet for three months with 15 patients who were recommended to follow a Mediterranean-like prudent diet with whole-grain cereals, low-fat dairy products, fruit, vegetables and refined fats generally considered healthy. All patients had increased blood sugar after carbohydrate intake (glucose intolerance), and most of them had overt diabetes type 2. In addition, all had been diagnosed with coronary heart disease. Patients in the Paleolithic group were recommended to eat lean meat, fish, fruit, vegetables, root vegetables and nuts, and to avoid grains, dairy foods and salt.

The main result was that the blood sugar rise in response to carbohydrate intake was markedly lower after 12 weeks in the Paleolithic group (–26%), while it barely changed in the Mediterranean group (–7%). At the end of the study, all patients in the Paleolithic group had normal blood glucose.

The improved glucose tolerance in the Paleolithic group was unrelated to changes in weight or waist circumference, although waist decreased slightly more in that group. Hence, the research group concludes that something more than caloric intake and weight loss was responsible for the improved handling of dietary carbohydrate. The main difference between the groups was a much lower intake of grains and dairy products and a higher fruit intake in the Paleolithic group. Bioactive substances in grains (e.g. wheat lectin) and dairy products (e.g. casein) have been shown to interfere with the metabolism of carbohydrates and fat in various studies.

If you want to prevent or treat diabetes type 2, it may be more efficient to avoid some of our modern foods than to count calories or carbohydrate >>.

This is the first controlled study of a Paleolithic diet in humans.

Comment in Science: http://www.sciencemag.org/content/vol317/issue5835/r-samples.dtl#317/5835/175c

http://www.staffanlindeberg.com/OurResearch.html

ESSENCE OF ARTICLE IS WHOLE ARTICLE.

Our main objective is to study nutrition in the prevention and treatment of cardiovascular disease and related metabolic disorders. The working hypothesis is that a Paleolithic diet (the Paleolithic is the time period 2,000,000-10,000 years BP), basically meat, fish, vegetables, fruit and nuts, has benefits even compared with prudent diets based on whole-grain cereals and low-fat milk.

The basic notions are that

1) foods are appropriate for any given species if they were regularly consumed during most of its prior evolution;

2) plants protect themselves with bioactive substances directly aimed at animals, substances which may have untoward effects on long-term human health.

Selected articles

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Original investigation

Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study

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ESSENCE OF ARTICLE

“The advice for patients with type 2 diabetes to follow a Paleolithic diet resulted in lower HbA1c, TG, DBP, weight and waist circumference, and higher HDL, as compared to a Diabetes diet according to current guidelines. In addition, fasting glucose and SBP tended to decrease more after the Paleolithic diet. Changes in glucose tolerance were not significantly different between diets. The two diets differed mainly in that the Paleolithic diet was lower in cereals and dairy products, and higher in fruits, vegetables, meat and eggs. Further, the Paleolithic diet was lower in total energy, energy density, carbohydrate, dietary GL, saturated fatty acids and calcium, and higher in unsaturated fatty acids, dietary cholesterol and several vitamins. Dietary GI was lower in the Paleolithic diet (GI = 50) than in the Diabetic diet (GI = 55).”

ARTICLE

Abstract

Background

Our aim was to compare the effects of a Paleolithic ('Old Stone Age') diet and a diabetes diet as generally recommended on risk factors for cardiovascular disease in patients with type 2 diabetes not treated with insulin.

Methods

In a randomized cross-over study, 13 patients with type 2 diabetes, 3 women and 10 men, were instructed to eat a Paleolithic diet based on lean meat, fish, fruits, vegetables, root vegetables, eggs and nuts; and a Diabetes diet designed in accordance with dietary guidelines during two consecutive 3-month periods. Outcome variables included changes in weight, waist circumference, serum lipids, C-reactive protein, blood pressure, glycated haemoglobin (HbA1c), and areas under the curve for plasma glucose and plasma insulin in the 75 g oral glucose tolerance test. Dietary intake was evaluated by use of 4-day weighed food records.

Results

Study participants had on average a diabetes duration of 9 years, a mean HbA1c of 6,6% units by Mono-S standard and were usually treated with metformin alone (3 subjects) or metformin in combination with a sulfonylurea (3 subjects) or a thiazolidinedione (3 subjects). Mean average dose of metformin was 1031 mg per day. Compared to the diabetes diet, the Paleolithic diet resulted in lower mean values of HbA1c (-0.4% units, p = 0.01), triacylglycerol (-0.4 mmol/L, p = 0.003), diastolic blood pressure (-4 mmHg, p = 0.03), weight (-3 kg, p = 0.01), BMI (-1 kg/m2, p = 0.04) and waist circumference (-4 cm, p = 0.02), and higher mean values of high density lipoprotein cholesterol (+0.08 mmol/L, p = 0.03). The Paleolithic diet was mainly lower in cereals and dairy products, and higher in fruits, vegetables, meat and eggs, as compared with the Diabetes diet. Further, the Paleolithic diet was lower in total energy, energy density, carbohydrate, dietary glycemic load, saturated fatty acids and calcium, and higher in unsaturated fatty acids, dietary cholesterol and several vitamins. Dietary GI was slightly lower in the Paleolithic diet (GI = 50) than in the Diabetic diet (GI = 55).

Conclusion

Over a 3-month study period, a Paleolithic diet improved glycemic control and several cardiovascular risk factors compared to a Diabetes diet in patients with type 2 diabetes.

Trial registration

ClinicalTrials.gov NCT00435240.

Background

While dietary management is a cornerstone in the treatment of type 2 diabetes, high quality data on the efficacy of dietary treatment of type 2 diabetes are lacking, according to a recent Cochrane review [1]. Since nutritional science is hampered by confounders, an evolutionary approach has been suggested. It has been postulated that foods that were regularly eaten during human evolution, in particular during the Paleolithic (the 'Old Stone Age', 2.5–0.01 million years BP), may be optimal for prevention and treatment of type 2 diabetes, CVD and insulin resistance [2,3]. A Paleolithic diet is a modern dietary regimen based on foods presumably eaten regularly during the Paleolithic, which includes lean meat, fish, shellfish, fruits, vegetables, roots, eggs and nuts, but not grains, dairy products, salt or refined fats and sugar, which became staple foods long after the appearance of fully modern humans.

To date, only a few studies have examined the effects of a Paleolithic diet on disease and risk factors for disease. In a randomized controlled study in 29 men with ischemic heart disease (IHD) and impaired glucose tolerance or type 2 diabetes (mean HbA1C 4.8% at baseline), we found improved glucose tolerance independent of weight-loss after 12 weeks of Paleolithic diet compared to a Mediterranean-like diet [4]. In the same study, the Paleolithic diet was reportedly lower in glycemic load (GL) than the Mediterranean-like diet [4]. The clinical relevance of glycemic index (GI) and GL is presently being discussed [5]. Some studies show beneficial effects of a low GI/GL diet on risk factors for CVD in diabetes, while other studies do not [6-8]. In a non-controlled study on 14 healthy individuals, Österdahl et al found that three weeks on a Paleolithic diet significantly reduced weight, BMI, waist circumference, systolic blood pressure (SBP) and plasminogen activator inhibitor-1 (PAI-1) [9]. In another non-controlled study in nine healthy overweight individuals where intervention food was supplied and weight kept steady, Frassetto et al found that ten days of a Paleolithic diet improved diastolic blood pressure (DBP), glucose tolerance, insulin sensitivity and lipid profiles [10]. In a randomized controlled feeding trial in domestic swine, we found higher insulin sensitivity, lower C-reactive protein (CRP) and lower DBP after 15 months of a Paleolithic diet, compared with a cereal-based swine feed [11]. This study also showed a low-grade inflammation of the pancreas in the swine who had eaten a cereal based swine feed [11]. In a non-controlled study of ten Australian Aborigines with diabetes and a mean BMI of 27 kg/m2, O'Dea found that reversion to a hunter-gatherer lifestyle during 7 weeks led to 10% weight loss and reductions in fasting and 2 hour glucose and fasting insulin [12]. In a similar study on healthy Australian Aborigines by the same authors, the insulin response to 70 g of starch from white bread was reduced, while the glucose response was not, after 10–12 weeks of reversion to a traditional lifestyle [13]. In an epidemiologic study, we found that traditional Pacific Islanders of Kitava, Papua New Guinea, had no signs of IHD, stroke or markers of the metabolic syndrome, possibly because of their traditional lifestyle [14-16]. Thus, we have previously shown beneficial effects from Paleolithic diet on glycemic control and risk markers for CVD in patients with IHD and in domestic pigs. No study, however, has so far examined the same potential beneficial effect of Paleolithic diet when compared to diabetes diet in subjects with type 2 diabetes.

In the present study, therefore, our aim was to examine the effect on glycemic control and risk factors for CVD of food-based (as opposed to macronutrient based) dietary advice according to this Paleolithic diet model over a 3-month period in patients with type 2 diabetes. The patients were recruited in a primary health care setting, and effects of a Paleolithic diet was compared with effects of dietary advice in accordance with current guidelines for people with diabetes [17].

Methods

Patients

Approval of the study was obtained from the regional Medical Ethics Committee and the trial was registered at ClinicalTrials.gov (Identifier: NCT00435240). The study was a randomized, cross-over, dietary intervention study in 13 patients with type 2 diabetes without insulin treatment, 3 women and 10 men, recruited from three primary health care units in the Lund area in Sweden. We included adult patients with type 2 diabetes and a C-peptide value above zero, unaltered medical diabetes treatment and stable weight since three months before start of study, HbA1c above 5.5% by Mono-S standard, creatinine below130 μmol/L, liver enzymes below four times their respective upper reference value, no chronic oral or injection steroid treatment and no acute coronary event or change in medication of beta blockers or thyroxin since six months before start of study. Exclusion criteria during ongoing study were change in beta blocker or thyroxin medication, chronic oral or injection steroid treatment, warfarin treatment, creatinine above 130 μmol/L or liver enzymes above four times their respective upper reference value, acute coronary event, and physical or psychological illness or changes in personal circumstances which would make further study participation impossible.

Recruitment for the study during routine clinical work was performed by TJ, UCB, GP, AH and MS. In addition, a letter containing written study information was sent by TJ to subjects at two of the health stations who from journal data seemed to match the inclusion criteria. All recruited subjects were given oral and written study information prior to signing a consent form to participate in the study and were then further assessed for eligibility.

Procedure

All eligible subjects were informed of the intention to compare two healthy diets in the treatment of type 2 diabetes and that it was unknown if any of them would be superior to the other. At study start all eligible subjects were randomized to start with either a Diabetes diet in accordance with current guidelines [17] or a Paleolithic diet. Randomization was performed by UCB, GP and AH by opening opaque, sealed envelopes (prepared by TJ) containing a note of the initial diet with equal proportions of envelopes for both diets. After randomization, there was no blinding of dietary assignment to study participants, nor to those administering the interventions or assessing the outcomes. Immediately after randomization, all subjects received oral and written information individually (by UCB, GP or AH) in the morning about their respective initial diet. After three months all subjects switched diets and received new oral and written information individually (by UCB, GP or AH) about the diet of the following three months. Written information with dietary advice and food recipes were similarly formulated for both diets. For increased conformity, the dietary advice and data collection procedure were discussed by all authors except YG at several meetings prior to start of study. Advice about regular physical activity was given equally to all subjects.

The information on the Diabetes diet stated that it should aim at evenly distributed meals with increased intake of vegetables, root vegetables, dietary fiber, whole-grain bread and other whole-grain cereal products, fruits and berries, and decreased intake of total fat with more unsaturated fat. The majority of dietary energy should come from carbohydrates from foods naturally rich in carbohydrate and dietary fiber. The concepts of glycemic index and varied meals through meal planning by the Plate Model were explained [18]. Salt intake was recommended to be kept below 6 g per day.

The information on the Paleolithic diet stated that it should be based on lean meat, fish, fruit, leafy and cruciferous vegetables, root vegetables, eggs and nuts, while excluding dairy products, cereal grains, beans, refined fats, sugar, candy, soft drinks, beer and extra addition of salt. The following items were recommended in limited amounts for the Paleolithic diet: eggs (≤2 per day), nuts (preferentially walnuts), dried fruit, potatoes (≤1 medium-sized per day), rapeseed or olive oil (≤1 tablespoon per day), wine (≤1 glass per day). The intake of other foods was not restricted and no advice was given with regard to proportions of food categories (e.g. animal versus plant foods). The evolutionary rationale for a Paleolithic diet and potential benefits were explained [19].

Evaluation

An oral glucose tolerance test (OGTT) was performed in the morning after obtaining venous blood samples and measurements of blood pressure, weight and waist circumference in the primary care unit (by UCB, GP or AH) at study start, after 3 months (when switching to a new diet) and at the end of the study (after 6 months). 75 g glucose was ingested. Blood samples for plasma glucose and insulin during OGTT were obtained at 0, 15, 30, 60, 90 and 120 minutes. Changes in the area under the curve (AUC) between 0 and 120 min during OGTT for plasma glucose (AUC Glucose0–120) and plasma insulin (AUC Insulin0–120) were predefined primary endpoints, along with changes in body weight, waist circumference, serum lipids, CRP, blood pressure and glycated haemoglobin A1c (HbA1c) by Mono-S standard. The base of the AUC was set at 0 mmol/L for glucose and 0 pmol/L for insulin. The stimulated secretion was represented by the areas under the glucose and insulin curves using levels at 0 min as the base of the area. The Homeostatic model assessment (HOMA) was used for assessing beta-cell function (%B) and insulin sensitivity (%S), as percentages of a normal reference population, and insulin resistance (IR, the reciprocal of %S (100/%S)) [20]. Values for %B, %S, and IR were derived from fasting plasma glucose and insulin using the HOMA2 computer model v2.2 [20]. Insulin sensitivity index (ISI0,120) was calculated from fasting (0 min) and 120 min (post-OGTT) insulin and glucose concentrations [21]. A 4-day weighed food record on four consecutive days, including one weekend day, with weighing of each food item on a digital weighing scale (that could be set to zero), was completed by the participants, starting 6 weeks after initiating each diet. Nutrient compositions were calculated by YG using data from The Swedish Food Database of the National Food Administration in Sweden. GL and GI for the two diets were calculated. Underlying concept of dietary GL and dietary GI is food GI, introduced by Jenkins et al [22], reflecting the postprandial glucose response after a specific food rich in carbohydrate, expressing the quality of the carbohydrates. Wolever and Jenkins also suggested the possibility of ranking diets based on dietary GI calculated from the proportional GI contribution of the included foods containing carbohydrate [23]. To include also the quantity of carbohydrates consumed GL was introduced by Salmerón et al expressing the glycemic effect of the diet [24]. While dietary GI is expressing the quality of the carbohydrates consumed GL represent both the quantity and the quality of the carbohydrates consumed. Thus, dietary GL in this study was calculated as the result from multiplying available carbohydrate (g) for the food reported by the subjects during the 4-day weighed food record with the specific food's GI divided by 100. Available carbohydrate was based on total carbohydrate minus dietary fibre. Food's GI values (glucose as reference) were taken from the compilation by Foster-Powel et al [25]. Dietary GI was calculated as 100 multiplied with dietary GL divided by the amount of available carbohydrate (g) in the diet.

Statistics

A pre-study power calculation showed that 15 subjects would be required to detect, with 80% power and at a significance level of 5%, a 15% reduction in AUC Glucose0–120. Two-way paired t-test was used to analyze within-subject changes in absolute values, while two-way unpaired t-test was used to analyze between-subject changes in absolute values. All outcome variables showed reasonable normal distribution in normal plots. Within-subject changes in outcome variables after first and second diet and within-subject changes in reported dietary intake during first and second diet were used to check for period effects [26]. Mean values of outcome variables and reported dietary intakes for the group starting with Paleolithic diet was compared with the group starting with Diabetes diet in order to check for carry-over effects [26]. Exploratory analyses were performed on outcome variables with significant effects from the Paleolithic diet as compared to the Diabetes diet. Exploratory analyses consisted of bivariate correlations between within-subject differences (Δ) in outcome and dietary variables. Significantly correlating variables were entered into a stepwise forward linear regression analyses.

Results

Recruitment and participant flow

The study started in January 2005 and the last participant was followed up in September 2007 after which the study was stopped. Out of 26 subjects assessed for eligibility, nine were not eligible since they did not meet the inclusion criteria or refused to participate. Out of the remaining 17 eligible subjects, who were all randomized and started on the study, four subjects were excluded for the following reasons: one starting with Paleolithic diet was wrongly included with ongoing warfarin treatment, one starting with Paleolithic diet was unwilling to continue due to abdominal pains and bloating, one starting with Diabetes diet was excluded after developing leukemia, and one starting with Diabetes diet was excluded after developing heart failure. All reported analyses are "per protocol" analyses on the 13 participants who completed the trial.

Medication

Study participants were on average treated with just above four drugs per day, which usually included metformin alone (3 subjects) or metformin in combination with a sulfonylurea (3 subjects) or a thiazolidinedione (3 subjects)(Table 1, 2). Medication usually also included a lipid lowering drug (8 of 13 study participants and always statin treatment) and more than one anti-hypertensive drug per day (Table 1, 2). All medication remained unchanged during the whole study with the following exceptions:

Table 1. Baseline characteristics (mean ± SD)

Table 2. Baseline differences and carry-over effects between groups with different starting diets (mean ± SD)

One participant stopped taking sulfonylurea (glibencklamide 87.5 mg daily) the day after starting the study with the Paleolithic diet, and was thus on a low dose sulfonylurea at baseline, but without sulfonylurea during both the Paleolithic and Diabetes diet. Exclusion of this participant would not negate any significant effects from the Paleolithic diet compared to the Diabetes diet, but would negate the effect from the Paleolithic diet compared to baseline on systolic blood pressure, and the effect from the Diabetes diet compared to baseline on BMI. Due to concerns for rising blood sugar levels one participant switched hypertensive treatment from a thiazide diuretic to a beta blocker for seven weeks during the Paleolithic diet. Exclusion of this participant would not negate the significant effect on HbA1c, but would negate the effect on diastolic blood pressure. Due to concerns about muscle ache one participant was without lipid-lowering drug treatment for four weeks during the Paleolithic diet. Exclusion of this participant would not negate the significant effects on TG and HDL, but would instead cause also total cholesterol to be significantly lower following the Paleolithic diet compared to the Diabetes diet ($p = 0.03$). One participant was put on finasteride (5 mg daily, a drug versus benign prostate hyperplasia) during the Paleolithic diet and continued this medication during the following Diabetes diet.

Baseline data

The group starting with the Paleolithic diet differed at baseline only with regard to fasting plasma glucose and AUC glucose being lower and HOMA2 %B being higher compared to the group starting with a Diabetes diet (Table 2). There was no difference between starting groups before or at the end of the study in inclusion/exclusion variables.

Outcome variables

Compared to the Diabetes diet, the Paleolithic diet resulted in lower mean values of HbA1c, TG, DBP, weight, BMI and waist circumference, while mean values for HDL were higher (Table 3, Figure 1). The larger decrease of fasting plasma glucose following the Paleolithic diet nearly reached significance, and SBP also tended to decrease more following the Paleolithic diet. Compared to baseline, the Paleolithic diet lowered mean values of HbA1c, TG, SBP, weight, BMI, waist circumference, fasting plasma glucose, fasting plasma insulin, AUC glucose, ISI0,120, HOMA2 %S and HOMA2 %IR (Table 3). Compared to baseline, the Diabetes diet lowered mean values of BMI, waist circumference and HOMA2 %S (Table 3). Period effects were seen in AUC insulin0–120, AUC insulin0–120 stimulated secretion and HOMA2 %B (Table 4). Carry over effects were seen in HbA1c (Table 2, Figure 1).

Table 3. Risk factors for cardiovascular disease after Paleolithic diet and Diabetes diet (mean ± SD, Confidence Interval 95%)

Table 4. Period effects on cardiovascular risk factors after 3 and 6 months in all 13 subjects combined (mean ± SD)

Figure 1. Cardiovascular risk factors with significant effects from Paleolithic diet compared to Diabetes diet. Closed circles depicts individuals starting with Diabetes diet first and open circles depicts individuals starting with Paleolithic diet first. Values are group means and error bars depicts SD for group means.

Reported food intake

There were no period or carry-over effects in reported dietary intakes (data not shown). Reported daily food intake differed between diets mainly in that the Paleolithic diet was markedly lower in cereals and dairy products, and lower in potatoes, beans and bakery, and much higher in fruits, vegetables, meat and eggs (Table 5). Further, the Paleolithic diet was somewhat lower in total energy, energy density, carbohydrate, fiber, saturated fatty acids and calcium, and higher in monosaccharides, dietary cholesterol, some vitamins (vitamin B6, vitamin C, niacin) and minerals (potassium, selenium) (Table 5). During the Paleolithic diet, there was a lower relative intake (as a percentage of total macronutrient energy intake [E%]) of carbohydrate and a higher relative intake of protein and fat (Table 5). Both dietary GL and dietary GI were determined to be lower for the Paleolithic diet than for the Diabetic diet (Table 5).

Table 5. Average food eaten per day during Paleolithic diet and Diabetes diet (mean ± SD)

Exploratory analyses

In exploratory analyses of primary endpoints, within-subject differences (Δ) in HbA1c (ΔHbA1c) correlated with Δwaist circumference, which correlated with Δweight, which correlated with ΔCRP (Table 6). Furthermore, ΔHDL correlated with Δcholesterol and ΔDBP with ΔHOMA2 IR (Table 6). In exploratory analyses of estimated intake of nutrients, ΔHbA1c correlated with Δpotassium, ΔHDL with Δfatty acid C20:5 n-3, ΔTG with Δthiamin, ΔDBP with Δdietary cholesterol, Δweight with Δenergy density per meal, and Δwaist circumference with Δbakery, Δenergy density per meal, Δsauce and Δvitamin E (Table 6).

Table 6. Exploratory analyses

Discussion

Key findings

The advice for patients with type 2 diabetes to follow a Paleolithic diet resulted in lower HbA1c, TG, DBP, weight and waist circumference, and higher HDL, as compared to a Diabetes diet according to current guidelines. In addition, fasting glucose and SBP tended to decrease more after the Paleolithic diet. Changes in glucose tolerance were not significantly different between diets. The two diets differed mainly in that the Paleolithic diet was lower in cereals and dairy products, and higher in fruits, vegetables, meat and eggs. Further, the Paleolithic diet was lower in total energy, energy density, carbohydrate, dietary GL, saturated fatty acids and calcium, and higher in unsaturated fatty acids, dietary cholesterol and several vitamins. Dietary GI was lower in the Paleolithic diet (GI = 50) than in the Diabetic diet (GI = 55).

Possible mechanisms and explanations

No advice was given to restrict food intake. Therefore, the lower reported energy intake during the Paleolithic diet despite no difference in weight of reported food intake agrees with the notion that such a diet is satiating and facilitates a reduced caloric intake [4,27]. Accordingly, energy density was lower in the Paleolithic diet and also correlated with alterations of both weight and waist circumference. The higher amount of fruit and vegetables during the Paleolithic period may have promoted weight loss due to its high content of water, which is thought to be satiating [28]. Interestingly, the Paleolithic diet appeared to be satiating despite a lower content of fiber in this study. The slightly higher relative protein intake, as percentage of total calorie intake, may also have added to a satiating effect [29,30]. Alternative explanations on satiation, such as dietary effects on leptin resistance, could also be considered [31].

A reduced energy intake would evidently be a major explanation for the beneficial effects of the Paleolithic diet on weight and waist circumference. Meta-analyses and large trials with various lifestyle interventions indicate that reduced caloric intake is more important for long-term weight loss than other known dietary factors, including macronutrient composition [32-40]. In studies shorter than 6 months, such as this one, differences in GI and/or GL may also have played a role for weight change. A Cochrane review found that overweight or obese people lost slightly more weight during 5–12 weeks of low GI diets [41], and short-term carbohydrate restriction possibly results in greater weight loss than low-fat diets [29]. However, dietary GI and dietary GL did not correlate with alterations of weight, waist circumference or metabolic variables in our study. It should also be noted that, in the present study, reported mean absolute carbohydrate intake in the Paleolithic diet (g per day) was only slightly below the 130 g per day recommended by the American Diabetes Association, and clearly above 50 g per day, which has been proposed as the level below which a diet should be termed a low carbohydrate diet [42].

Paleolithic diet improved the glycemic control in the subjects, as evident by the reduction of HbA1c levels by -0.4 percentage points lower as compared to the diabetes diet. Since both glucose and insulin levels declined during Paleolithic diet, a main mechanism behind the improved glycemic control is probably improved insulin sensitivity, which may have allowed the released insulin to work more efficiently. The difference in reduction in HbA1c of 0.4% units between the Paleolithic and Diabetes diet is close to the average 0.5% units in a recent Cochrane review of diets with a low glycemic index or glycemic load [8]. However, the differences in GI between diets in that meta-analysis were considerably larger than in our trial. Glucose tolerance, which also determines the glucose response and thereby HbA1c, did not improve more during the Paleolithic diet. This result agrees with findings from Frassetto et al [10], but differs from our previous parallel-group trial which compared a Paleolithic diet with a Mediterranean-like diet in subjects with diabetes or impaired glucose tolerance [4]. Glucose tolerance has not been shown to improve after reduced carbohydrate intake in earlier dietary studies [43-46].

The much higher fruit intake of the Paleolithic diet probably resulted in a slightly higher intake of fructose which may have aided in the reduction of HbA1c. Fructose in exchange for starch, sucrose or glucose decreases postprandial glycemia [47], while the effect on glucose tolerance and insulin sensitivity is more uncertain [48]. The effect of fruit on TG and other risk factors is expected to have been neutral in this study [48,49]. Total intake of monosaccharides was 46 g per day, including approximately equal amounts of glucose and fructose, which was well below the suggested safety limit of 50 g fructose per day [48]. Our study lends further support to the notion that fruit intake should not be restricted in patients with type 2 diabetes.

The lower DBP after the Paleolithic diet compared to the Diabetes diet did not correlate with sodium intake, which did not differ significantly and was rather low in both diets (2.5 g and 3.0 g per day respectively for the Paleolithic and Diabetes diet).

The reduction of TG after the Paleolithic diet was possibly due to greater loss of abdominal fat [50] or lower GL compared to the Diabetes diet [6], although no correlation of TG with waist loss or GL was seen in exploratory analyses. A small additional effect on TG may be attributable to a trend for higher content of long-chain omega-3 fatty acids in the Paleolithic diet, while the higher dietary cholesterol content of the Paleolithic diet is probably of minor significance [51].

Comparison with findings from other studies

All improvements in markers of the metabolic syndrome on the Paleolithic diet are in line with findings from epidemiological studies in non-Western populations [14-16]. Improvements in HbA1c [4], weight [4,12,52], BMI [52], waist circumference [4,52], DBP [10], and TG [10], compared to baseline, on a Paleolithic diet have been observed before in intervention studies, while improvements in HDL have not. Similar differences in weight and DBP on a Paleolithic diet, compared to a cereal based diet, have been observed before in an intervention study on domestic pigs [11]. A lower reported energy intake and energy density of food despite food intake ad libitum agrees with our earlier findings that a Paleolithic diet facilitates a reduction of caloric intake [4,11,27].

Also, lower intake of cereals, dairy products, carbohydrates, dietary GL and saturated fat, and higher intake of fruit and potassium have been observed before [4,10]. Lower intake of potatoes, bakery, fiber, phosphorous and calcium, and higher intake in vegetables, meat, eggs, monosaccharides, dietary cholesterol, vitamin B6, vitamin C, niacin and selenium have not been observed before in intervention studies with a Paleolithic diet. Dietary GI for a Paleolithic diet has not been determined before.

Limitations of the present study

A limitation of this study, as with most other dietary trials, is the lack of blinding after randomization. To minimize this problem, all study participants were informed of the intention to compare two healthy diets in the treatment of type 2 diabetes and that it was unknown if any of them would be superior to the other. Also, written information with dietary advice and food recipes were similarly formulated for both diets. Furthermore, for increased conformity, the dietary advice and data collection procedure were discussed by all those administering the interventions at several meetings prior to start of study.

Another limitation of this study is its small size which did not reach the number of participants needed as calculated in the pre-study power calculation. The decision to end the study was taken when recruitment for the study had not yielded new participants for more than six months. The population of patients with type 2 diabetes is much larger and therapy continues for substantially longer than in this study. Moreover, many patients with type 2 diabetes have illnesses and treatments that excluded them from the current study. Consequently, the results of this study do not address the occurrence of rare adverse events, nor can they be extrapolated to all patients seen in general clinical practice.

The carry-over effects on HbA1c were not due to carry-over or period effects in reported food intake. Instead, they could be true carry-over effects of the first diet. This is particularly likely for HbA1c, since HbA1c represents a weighted average of the blood glucose concentration over the previous two to three months ([53]. If results from the second period were discarded (owing to carryover [54]), the reduction of HbA1c from the Paleolithic diet compared to the Diabetes diet was still significant ($p = 0.01$) and even larger (-1.3% units) than when results from the second period were included. However, this approach could lead to biased answers to our hypothesis and results from both periods are therefore used in this study [54].

The lack of carry-over or period effects in reported food intake indicates fairly good adherence to intervention diets. Reported food intake in this study seemed reasonable both in distribution and quantity, as subjectively assessed by a nutrition engineer skilled in analyzing reported food intake (YG). Furthermore, the reported lower energy intake of 1.3 MJ per day on a Paleolithic diet equals about 3.2 kg fat during three months, which almost exactly accounts for the observed 3.3 kg difference in weight loss between diets. This indicates both good reporting by the participants and good adherence to reported food intake during the study.

Clinical and research implications

The favourable results in this study are in line with previous findings and increase the generalizability of the Paleolithic diet by testing it in both men and women in a primary care setting. A limitation of the study is the small size of the study population. This prevents the conclusions from resulting in nutritional recommendations for patients with type 2 diabetes. A long-term study in a larger population is therefore required. In parallel, further research into possible mechanisms for the beneficial effects of a Paleolithic diet should be done.

Total protein intake in g per day did not differ between the diets, but, as a result of the difference in total energy intake, the energy percentage (E%) from dietary protein on the Paleolithic diet (24 E%) slightly exceeded US and European recommendations for people with diabetes (<20 E%) [17,55]. The debatable disadvantage for long-term kidney function [56,57] should be weighed against the benefits of attenuated postprandial glycemia when protein replaces starch or glucose [58].

Calcium intake did not meet recommendations for any of the diets, and it was particularly low in the Paleolithic diet. Recent calcium balance studies indicate that human calcium requirements are lower than previously thought [59], and meta-analyses of randomized controlled trials suggest that the effect of calcium supplementation for bone strength is limited [60,61]. It has been suggested that absorption and excretion of calcium are more important than calcium intake for whole-body calcium balance [62]. In this context, the lower content of calcium-binding phytate and the lower dietary acid load from a Paleolithic diet may hypothetically compensate for the low amount of calcium [63]. Supporting this view are the findings of Frassetto et al, where calcium intake remained unchanged and urine calcium decreased after a Paleolithic diet compared to baseline [10].

As has been discussed, there may be a challenge to implement and adopt the Paleolithic diet on a worldwide scale in subjects with type 2 diabetes. However, this aspect is beyond the objective of this paper and requires more research.

Conclusion

Based on the results of this 3-month randomized cross-over study in subjects with type 2 diabetes, a Paleolithic diet improves glycemic control in association with improvement of several cardiovascular risk factors compared to a conventional diabetes diet. The study supports the initiation of a large scale study on the effect of Paleolithic diet in subjects with type 2 diabetes.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TJ participated in the design and execution of the study, participated in statistical analysis, and conceived of and wrote the article. YG analyzed reported food intake and participated in the design of the article as well as revising it for important intellectual content. BA participated in the design of the study, carried out the analysis of glucose and insulin in OGTTs, and revised the article for important intellectual content. UCB, GP, AH and MS participated in the design and execution of the study, and revised the article for important intellectual content. SL participated in the design of the study, participated in statistical analysis, and participated in the design of the article as well as revising it for important intellectual content. All authors read and approved the final manuscript.

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