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Honey as a Sole Treatment of Type 2 Diabetes Mellitus

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Abstract

Objectives: The complications from type 2 diabetes mellitus (DM) still occur despite the ongoing efforts to prevent, or decrease it. This clinical trial aimed to evaluate the effects of honey, as an alternative, non-expensive natural substance in twenty adult patient volunteers suffering from type 2 DM and its associated metabolic derangements.

Methods: The patients volunteered to stop the medicines and use honey as a sole treatment of their illnesses. There was no specific dietary restriction except for food preservatives and additives, beverages and sweets.

Results: Honey consumption resulted in more hyperglycemia in these patients, but without diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS). Longer-term honey consumption resulted also in weight reduction in all the patients, and control of the blood pressure in the patients, who had hypertension before the honey intervention. The median duration of the honey intervention, without anti-diabetic medicines was 1.09 years, with a range from 0.42 to 13.5 years. Ten of the 20 patients continued the honey intervention for more than 1 year, whereas the other 10 continued the intervention for one year or less. The only cause of the discontinuation of the honey intervention was persistent hyperglycemia. Despite persistent hyperglycemia in all the patients, and persistence of the dyslipidemia in the patients, who had dyslipidemia before the intervention, the macro-vascular complications, particularly the coronary heart disease (CHD), did not develop in any of them. On the contrary, the cardiovascular status improved in the patients, who had CHD before the intervention. However, micro-vascular complications developed in two patient volunteers, who continued the honey intervention, without medicines, for more than 8 years.

Conclusion: The author imposed on announcing these results, which might be of help for the patients with diabetes mellitus.

Keywords: Honey; Diabetes mellitus; Metabolic syndrome; Obesity; Hypertension; Dyslipidemia; Coronary heart disease

Abbreviations

ALT: Alanine Aminotransferase; Apo A-1: Apo lipoprotein A-1; Apo B: Apo lipoprotein B; BMI: Body Mass Index; BUN: Blood Urea Nitrogen; CHD: Coronary Heart Disease; CK-MB: Creatine Kinase-MB; CVD: Cardiovascular Disease; DKA: Diabetic Ketoacidosis; DM: Diabetes Mellitus; ECG: Electrocardiogram; FBG: Fasting Blood Glucose; HbA1C: Glycosylated Hemoglobin; HDL: High Density Lipoprotein; HHS: Hyperglycemic Hyperosmolar State; HTN: Systemic Hypertension; LDL: Low Density Lipoprotein; PPG: Post Prandial Glucose; RBG: Random Blood Glucose; TC: Total Cholesterol; TG: Triglycerides

Background

In spite of recent advances in the management of Diabetes Mellitus (DM) the mortality from macro-vascular complications, particularly Coronary Heart Disease (CHD) is still high. The prognosis in patients with diabetes mellitus is strongly influenced by the degree of control of their disease. Chronic hyperglycemia is associated with an increased risk of micro-vascular complications, as shown in the United Kingdom Prospective Diabetes Study (UKPDS) in people with type 2 diabetes [1]. However, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT), showed no improvement in cardiovascular disease and death with tight glycemic control [2-4]. For many decades, researchers have been trying to solve the puzzles surrounding the pathogenesis of diabetes and its complications, aiming at achieving the main goal; prevention or remission of diabetes; or at least prevention of its complications. These complications are responsible for not only significant morbidity and mortality, but also for a large economic burden. For this; several treatment strategies, including drugs, have been used in DM to control hyperglycemia and other associated metabolic derangements; and to treat the complications particularly CHD. However, the control of hyperglycemia and dyslipidemia, at least in some patients, has failed to prevent or reduce these complications.

Honey, a natural substance produced by honey bees, has many benefits for health which is universally acknowledged since time immemorial. Moreover, honey is not expensive. Honey as an emerging novel anti-diabetic agent has been recently recognized in several studies [5-11], suggesting that honey, through its anti-oxidant [12-14], anti-microbial [15-19], immune modulator [20] and anti-

inflammatory effects [21-24] might have the potential to act as a multi-targeted agent in patients with DM.

The author has started practicing using honey in treatment of diseases, especially respiratory and gastrointestinal diseases since 1999. In 2001, the author asked his friend, who is a dermatologist, aged 50 years, having type 2 DM of 9 years duration, and having hypertension, dyslipidemia and obesity, to make for him a sugar tolerance curve, using honey instead of glucose. On the day of the test, he did not receive his oral hypoglycemic drugs, and then he received 75 g honey dissolved in water, and the blood glucose levels measured every 30 minutes for 2 hours. The blood glucose readings were 135, 240, 261, 237 and 146 mg/dl at 0, 30 min, 60 min, 90 min and 120 min, respectively. On this day, after the test, he did not receive his oral hypoglycemic drugs. Next day morning, his fasting blood glucose level was 123 mg/dl. Then the author said to him," let us again giving honey without anti-diabetic medications and follow your blood glucose levels". Next day, he also received 75 g honey without anti-diabetic drugs. His blood glucose levels in this day ranged from 150 to 220 mg/dl, which were nearly similar to the levels with the oral hypoglycemic drugs. Thereafter, the dose of oral honey increased to almost 150 gm/day, and he remained on this dose without oral hypoglycemic drugs for almost two months, waiting for the possible control of his blood glucose. During these 2 months-honey intervention without oral hypoglycemic drugs, his general condition remained stable, and his random blood glucose levels ranged from 150 to 285 mg/dl. However, when his blood glucose started to rise above 350 mg/dl, he stopped the honey and resumed his oral hypoglycemic drugs. During this period of the honey intervention, repeated urine tests were negative for acetone despite polyuria and decreased body weight from 116 kg to 110 kg. Similar results were obtained in other patient volunteers, who continued the honey intervention for less than 3 months. These preliminary results made the author construct a study design to evaluate the effects of longer term consumption of large doses of honey, as a sole treatment, in a group of adult patient volunteers suffering from diabetes mellitus.

In November, 2013, author reported in the journal of clinical trials a case of Coronary Heart Disease (CHD), hypertension and type 2 DM, who stopped his medicines and used honey as an alternative therapy for almost 11 years [25]. In spite of persistent hyperglycemia and dyslipidemia, unexpectedly, his blood pressure was controlled, his CHD improved or at least stabilized. Further, he did not develop cerebral strokes. Moreover and unexpectedly, he did not develop diabetic ketoacidosis (DKA) or hyper-osmolar coma (HHS). However, he developed micro-vascular complications in the form of peripheral neuritis and non-proliferative retinopathy after 6 and 8 years, respectively. Although a final conclusion could not be drawn from a single case, this case study highlighted important observations and questions that warrant well designed studies in a large cohort of patient volunteers to test the benefits of honey as a sole treatment of type 2 DM versus the risks.

In the present study, the effects of long term use of honey as a sole treatment of type 2 DM were evaluated in a group of adult patient volunteers. The design of the present study was planned according to the preliminary results obtained in the first patients enrolled.

Subjects and methods

Eligibility

Eligible patient volunteers fulfilled the following inclusion and exclusion criteria:

Inclusion criteria

Adult patients with type 2 DM, who volunteered to stop their medicines and use honey as a sole treatment of their illnesses. The age of the participants ranged from 30 to 65 years, and they were of both sexes.

Exclusion criteria

The exclusion criteria included patients with renal failure, heart failure, liver cell failure, cancer, connective tissue diseases, other endocrine disorders, or psychiatric disorders. Also, illiterate patients, critically ill patients due to any disease, and pregnant or lactating women were excluded.

Design

The present study was a non-randomized, open clinical trial, which aimed to study the safety and efficacy of honey, as a sole treatment, in a group of patient volunteers with type 2 diabetes mellitus (DM). The study was a single arm phase I cohort prospective study. In phase I clinical trials the researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. A single arm or group/cohort study is a study that consists of only a single group of subjects included in the study design, in which all subjects received a single intervention and the outcomes are assessed over time. Single group study designs are commonly used to monitor adverse events that may become evident only with long-term follow up of treated patients, which is not practical or efficient with other study designs. Prospective studies follow participants forward through time. They are less prone to bias and can more easily demonstrate that the exposure preceded the disease, thereby more strongly suggesting causation. The primary endpoint of this study was binomial. Only two possible outcomes: complications or no complications. The end point of the study, and hence the duration of the study, was based on safety/efficacy. Because it was not known whether honey with its high sugar content as a sole treatment of type 2 DM will result in negative or positive effects, there was one of three possibilities for the estimation of the endpoint of this study: First, if negative effects, the short-term complications of type 2 DM and its associated disorders, particularly CHD, are expected to occur within hours or days after the start of the honey intervention. If this happened, the study will be terminated and the patient will be managed by the traditional way. Second, if positive effects, the endpoint will be at least 1 year after normalization of blood glucose provided no complications. Third, to prove the safety and efficacy of an intervention in type 2 DM with regard of the long-term complications, the study should continue for life or for at least 20 years provided the blood glucose levels are not normalized and the short term complications did not develop. If any of the long term complications developed, the onset and the severity of the complication or complications will then be compared with those of the patients on the traditional treatment, and the decision to continue or terminate the study will depend on the result.

From the current scientific point of view, this study design is not suitable for patients with diabetes, obesity, hypertension, CHD and dyslipidemia. However, the unexpected positive preliminary results made author and the patient volunteers participate and continue the trial, waiting for the possible disease remission.

Intervention

The patient volunteers stopped their medicines and took honey in an empirical dose of 2 g/kg/day, assuming body weight 75 kg i.e., 150 g (125 ml) honey daily. The daily honey dose was divided as 50 ml (60 g) honey dissolved in water (with a ratio of 1:3, respectively) and given before meals twice daily; and the remaining 25 ml (30 g) was used for sweetening purposes. Dissolving honey in water enhances the anti-microbial properties of honey [15,16], facilitates swallowing and helps adjusting the dose. There was no specific dietary restriction except for food preservatives and additives, beverages and sweets. Further, the total calories provided by this amount of honey (150g × ~ 3 = ~ 450 calories) were not subtracted from their meals. Also, the patients were asked to use honey as the only sweetening agent, and to double or triple the daily dose during any infection.

The honey was prescribed to the patients in an empirical large dose because; first, reported toxicity from consumption of large doses of honey does not exist. Honey is generally safe, except probably for infants under the age of 1 year because of the possible existence of *Clostridium botulinum* spores. Thus, recommended honey doses are not required for safety purposes. Second: There is no a solid scientific basis of this dose. However, the author have practiced using honey as a medicine in different diseases, especially respiratory and gastrointestinal diseases, since 1999 until today (almost 16 years), and he have observed that larger doses of honey have a more therapeutic effect than smaller doses. Therefore, author used to increase the dose of honey when the therapeutic response is not adequate. This observation has a historical, religious background in Islam. In Sahih Muslim; Chapter 29, Book 26, Number 5492:

Abu Sa'id Khudri reported that a person came to Allah's Apostle (may peace be upon him) and told him that his brother's bowels were loose. Thereupon Allah's Messenger (may peace be upon him) said: Give him honey. So he gave him that and then came and said: I gave him honey but it has only made his bowels looser. He said this three times; and then he came the fourth time, and he (the Holy Prophet) said: Give him honey. He said: I was giving him, but it has only made his bowels looser, whereupon Allah's Messenger (may peace be upon him) said: Allah has spoken the truth and your brother's bowels are in the wrong. So he made him drink (honey) and he was recovered. This hadith has been narrated on the authority of Abu Sa'id Khudri through another chain of transmitters but with a slight variation of wording.

Apart from the food preservatives and additives, beverages and sweets, this study did not include a specific dietary restriction or a food plan. However, there is no a current scientific source of these dietary instructions, but these instructions were based on the preliminary results discovered, by chance, in the first patients enrolled, who showed a reduction of their body weight with the honey consumption, without specific diet restrictions. The rate of weight loss was higher during the first months of the study, especially during periods of increased polyuria.

Honey

Three types of honeys were used in this study. Clover and Citrus honey from Egypt, and Ziziphus honey from Yemen and Pakistan. The honey used was a raw, unprocessed (not heated or irradiated) honey, freshly collected from an apiary, and then kept in dark containers at room temperature. Physicochemical analysis of some honey samples showed a specific gravity of 1.39 - 1.44, a moisture content of 14 - 20.8%, pH of 3.45 - 4.3, electrical conductivity of 0.29 - 0.82 mS/cm, a reducing sugar content >67 g/100 g, a sucrose content <3 g/100 g, a mean fructose to glucose ratio of 1.25:1, respectively and a Hydroxy Methyl Furfuraldehyde (HMF) content <15 mg/kg. Values of HMF less than 15 mg/kg indicated fresh honey not exposed to heat [26]. Microscopic examination of honey samples confirmed the presence of pollen grains.

Outcome measures

The primary outcome measure is composite; the clinical condition with regard of general condition, body weight, signs of dehydration, vital data (pulse and respiratory rate), blood pressure, exercise tolerance, neurological abnormalities, peripheral extremities and vision are the main outcome measures. The secondary outcome measures were the blood glucose levels, the HbA1C, the urine ketones and albumin, the serum lipids, the serum creatinine, the blood urea, the urine albumin/creatinine ratio, the ALT, the blood count and hematocrit, the ECG and the Doppler Echocardiography.

Follow-up and monitoring of patients

Monitoring of the patients was done on a daily basis through face-to face- appointment and telephone communication. In the case the study was not terminated, the frequency of monitoring was changed, based on the patient's condition. The follow-up plan consisted of measurement of random blood glucose (RBG) and doing urinalysis every day or every other day, measurement of HbA1C every 3 months, and measurements of serum lipids, urine albumin/creatinine ratio, renal functions, ECG and Doppler Echocardiography every year unless the patient's condition necessitated more frequent assessments. Eye and fundus examination was done every 3 to 6 months or at more frequent intervals if the patient started to complain of any eye disorder. In general, the frequency of monitoring was apt to change depending on the patient's condition. Measurements of urine ketones, arterial or venous pH, serum bicarbonate, anion gap, serum electrolytes, and serum osmolality were done whenever there was a suspicion of DKA or Hyperosmolar hyperglycemic state (HHS); positive urine test for ketones and clinical signs suggestive of DKA or HHS. If the hyperglycemia was worrisome, especially when the patient started to develop marked polyuria, polydipsia and loss of weight, the urine will then be tested for ketones. Also, measurements of pH, serum osmolality, serum bicarbonate and anion gap may be done to detect DKA or hyperglycemic hyperosmolar state (HHS) at an early stage before the development of any disturbance of the level of consciousness. At this point the study will be stopped and the patient will be managed by the traditional way.

Ethical considerations

Informed verbal consent was obtained from each patient before the study. Prior to the consent, each patient volunteer was clearly informed of the details of the study and the potential risks and benefits. The

patients had the right to refuse or withdraw the intervention at any time.

Enrolled in this study are educated adult patients, who know very well the nature of their diseases and the sequelae of uncontrolled diabetes. They also know how to manage their blood glucose levels without consulting their doctors. Further, they know that honey contains large amounts of sugars and is not advised to be given in large amounts in diabetic patients. Therefore, there was a reservation from the patients when author asked for a signed consent because they already know that this study is potentially risky. The author just reported to them the preliminary results with the first volunteers. The encouraging results were the body weight reduction without diet restriction, and the absence of coma in the face of the persistent hyperglycemia, but the discouraging result was the increasing hyperglycemia.

The author did not ask for approval from the ethical committee because he did not expect that any ethical committee will accept this risky clinical trial, which involves stoppage of medicines in the patients with diabetes, and substitution by honey, which is composed mainly of carbohydrates.

Potential risks

It is not known whether honey with its high sugar content, as a sole treatment of type 2 DM, will result in negative or positive effects. Therefore, the progress of this study will depend on the results. First, if negative effects, the short-term complications of type 2 DM are expected to occur within hours or days. In this situation, the study should be terminated and the patient will be managed by the traditional way. If the hyperglycemia persisted and the patient started to develop polyuria, polydipsia or loss of weight, the urine will then be tested for ketones. Also, measurements of pH, serum osmolality, serum bicarbonate and anion gap may be done to detect DKA or HHS at an early stage before the development of any disturbance of the level of consciousness. If DKA or HHS developed, the honey intervention will be stopped, and the patient will be managed by the traditional way. If the blood glucose levels are not controlled and no short term complications developed, then the study will continue for a longer time to test the effects of the intervention on the long term complications. If any of the long term complications developed, the onset and the severity of the complication or complications will then be compared with those of the patients on the traditional management, and then the decision to continue or terminate the study will depend on the result. Second, if positive effects, the endpoint of the study will be at least 1 year after normalization of blood glucose provided no complications.

Potential benefits

It includes substitution of drugs by natural products, with the possible additional benefits of preventing or at least reducing the complications of diabetes, and hence decreasing the economic burden.

Sample size and power of the study

The primary endpoint of this study is binomial i.e., only two possible outcomes; complications or no complications. Assuming the honey intervention will result in early complications in 99% of the volunteers, and the incidence of complications of the disease and the prescribed drugs in the general population with diabetes is 50 %, then using post-hoc test to determine the statistical power, a sample size of at least 10 patients will yield a statistical power of 100% at $\alpha = 0.05$.

Results

From 2001 until today, 38 eligible patient volunteers were enrolled. Their age ranged from 33 to 64 years, with a mean age of 48 years. Of the 38 volunteers, 20 patients continued the honey intervention, without anti-diabetic medications, for more than 3 months, whereas 18 patients discontinued the intervention before 3 months because of persistent hyperglycemia. The data of the patients, who continued the honey intervention, without anti-diabetic medications, for more than 3 months, from 2001 until March 2016, are presented here and included in the final statistical analysis. Table 1 shows the demographic data of the 20 patient volunteers, and Table 2 shows the baseline characteristics of these patients: The age ranged from 36 to 59 years [mean (± SD) = 46. 3± (6.1) years] and they were of both sexes (M:F = 3:2). The duration of diabetes ranged from 0.08 to 15 years [mean (±SD) = 5.3 ± (3.9) years]. Fourteen (70%) patients were receiving oral hypoglycemic drugs, four (20%) were insulin treated and two were not receiving medicines; one was on diet control and the second patient was receiving oral honey as an alternative treatment for her chronic hepatitis C. The HbA1C values ranged from 7.1 to 13.6 with a mean (SD) of 9.7 (±1. 9). Nine (45%) patients had their HbA1C value ≥ 10; four had HbA1C < 8; and 7 had HbA1C 8 < 10%. The BMI ranged from 23.7 to 56.1 [mean (± SD) = 32.6 (±6.7)]. All the patients, except one, were either overweight or obese; twelve (60%) patients had their BMI above 30. Twelve (60%) patients had systemic hypertension, and 12 (60%) had dyslipidemia. Twelve (60%) patients had symptoms of peripheral neuritis, and one patient had retinopathy with retinal hemorrhage. Four patients had coronary heart disease (CHD); with stents implanted in the coronary arteries for two of them.

No.	Name	Sex	Age (yr.)	BMI before the intervention	Diseases	Duration of the honey intervention (yr.)
1	SS	M	48	27.8	T2DM; HTN; Dyslipidemia; CHD	13.5
2	TA	M	47	34.5	T2DM; HTN; Dyslipidemia; CHD	6
3	RS	F	46	28.6	T2DM; Dyslipidemia; Chronic hepatitis C	2.6
4	RH	F	36	36.4	T2DM; Dyslipidemia; CHD	4
5	MA	F	50	32.5	T2DM; HTN; Dyslipidemia	9.3
6	FH	F	52	56.1	T2DM; HTN; Dyslipidemia	0.42

7	AE	M	37	23.7	T2DM	0.6
8	SO	F	43	32.8	T2DM; Dyslipidemia	1.75
9	KA	F	48	32.7	T2DM; HTN; Dyslipidemia	1.1
10	MR	M	48	33.2	T2DM; HTN; Dyslipidemia	2.6
11	TJ	M	43	32.7	T2DM	1
12	MZ	M	56	27.9	T2DM; Dyslipidemia	1.33
13	HA	M	53	31.3	T2DM; HTN; Dyslipidemia; CHD	0.7
14	MS	M	40	37	T2DM; HTN	0.6
15	ML	M	43	27.9	T2DM; HTN	0.58
16	KM	M	51	28.6	T2DM	1
17	AK	M	43	36.9	T2DM	1.08
18	EF	F	40	36.5	T2DM; HTN; Dyslipidemia	1
19	YA	M	42	27.9	T2DM; HTN	1
20	AA	F	59	26.7	T2DM; HTN; chronic hepatitis C	2

Table 1: Demographic data of the 20 patient volunteers. BMI: Body Mass Index; T2DM: Type 2 Diabetes mellitus; CHD: coronary Heart Disease; HTN: Hypertension.

Characteristic	
Age (yr.)	
Mean ± SD Range	46.3 ± 6.1 37 - 59
M: F	3:2
Duration of diabetes (yr.)	
Mean ± SD Range	5.4 ± 3.7 0.08 - 15
BMI (kg/m^2) Mean± SD	 32.6 ± 6.7
Anti-diabetic therapy	
Oral hypoglycemic drugs [No. (%)] Insulin [No. (%)] No medicines [No. (%)]	14 (70%) 4 (20%) 2 (10%)
Blood pressure (mmHg)	
SBP (mean ± SD) [range]	135.5 ± 19.3 [105 - 170]
DBP (mean ± SD) [range]	87.3 ± 10.1 [70 - 110]
Hypertension [No. (%)]	12 (60%)
Peripheral neuropathy [No. (%)]	12 (60%)
Coronary heart disease [No. (%)]	4 (20%)
Retinopathy [No. (%)]	1 (5%)

Hb A1C %	
Mean ± SD	9.7 ± 1.9%
TG	
Mean ± SD [range]	193.4 ± 106.1 [86 - 424]
TC	
Mean ± SD [range]	206.6 ± 50.1 [118 - 313]
HDL	
Mean ± SD [range]	45.2 ± 7.8 [33 - 57]
LDL	
Mean ± SD [range]	127.2 ± 39.2 [60 - 186.2]
Dyslipidemia [No. (%)]	12 (60%)

Table 2: Baseline characteristics of patients (20 patients). Yr.: year; SD: Standard Deviation; BMI: Body Mass Index; No.: Number; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HbA1C: Glycosylated hemoglobin; TG: Triglycerides; TC: Total Cholesterol; HDL: High Density Lipoprotein; LDL: Low density lipoprotein.

The duration of the honey intervention from 2001 to 2016 ranged from 0.42 to 13.5 years, with a median (IQR) of 1.09 (1.75) years. Ten (50%) patients continued the honey intervention for more than 1 year, 5 patients (25%) completed one year intervention, and 5 (25%) discontinued the intervention before one year (Figure 1). In the 10 patients, who continued the trial for more than 1 year, the period of the intervention ranged from 1.08 to 13.5 years, with a median (IQR) of 2.6 (4.25) years. Of these 10 patients, 2 patients are still on the honey therapy alone, without medications until today, 2 patients are receiving honey along with the anti-diabetic medicines until today, whereas 6 patients discontinued the honey intervention and resumed their medicines. Only the data during the period of the honey intervention alone, without medicines, were included in the final analysis. The only cause of the discontinuation of the honey intervention was persistent hyperglycemia. Two patients, SS and MA, completed until today 13.5 and 9.3 year honey intervention without anti-diabetic medications.

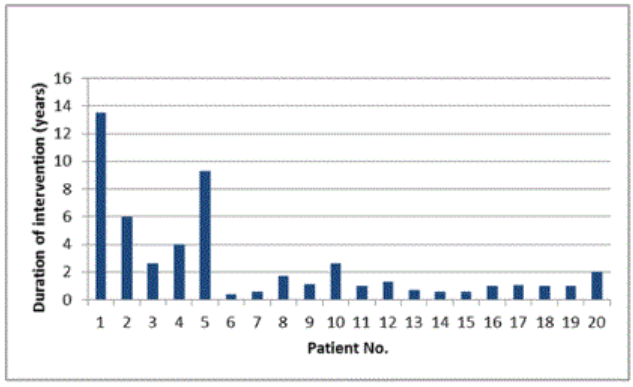


Figure 1: The duration of the honey intervention in the twenty patient volunteers with type 2 diabetes mellitus. Range = 0.42 - 13.5 years; Mean = 2.76 years; Median = 1.09 years.

Blood glucose changes

During the first weeks of the study, 19 (95%) patients developed, in addition to persistent hyperglycemia, polyuria, polydipsia and loss of weight. In all the patients the urine was negative for ketones. Testing the urine for acetone was done for all the patients every day or other day during the first 2 months of the study, with negative results. Further, measurements of pH, serum osmolality, serum bicarbonate, serum electrolytes and anion gap, done for some patients, did not also reveal any abnormality. Analysis of the results of blood glucose measurements in the 20 patients during the first year of the study found that the random blood glucose (RBG) before the study ranged from 93 to 430 mg/dl, with a mean (±SD) of 277 (±86.2), compared to 62 to 667mg/dl, with a mean of 373.8 (±86.3) during the first year of the study. This difference was statistically significant ($p = 0.001$) (Figure 2).

In 18 (90%) patients the RBG started to rise above the baseline values after a median of 4 days, with a range from 1 to 30 days. One patient, TJ, however, remained with nearly normal blood glucose levels during the first 9 months of the study (RBS ranged from 62 to 212 mg/dl; with a mean of 110.2 ± 43.1 mg/dl), and his body weight increased from 89 to 93 kg. Thereafter, he started to develop marked hyperglycemia with RBG frequently exceeding 400 mg/dl and he started to lose weight (his weight dropped from 93 to 77.5 kg during the next 4 months). The second patient, AA, continued the honey intervention for almost 2 years. Throughout this period, her RBG remained nearly within the same range as before starting the intervention. This patient was the only patient, who was receiving honey before the development of diabetes. This female patient, aged 55 years, has had hepatitis C since January 7, 2007. She started to receive honey on August 1, 2008, as an alternative treatment for her chronic hepatitis C. The baseline characteristics of this patient are shown in Table 3. The oral dose of honey was 50 ml (60 g) honey dissolved in water and consumed before meals twice daily. She continued the honey, as a sole treatment, until April, 2014. She developed diabetes mellitus (DM) in April, 2012. The changes in the characteristic values between 2008 to March, 2012, and between April, 2012 and the end of

the study, April, 2014 are shown in Tables 4 and 5. Throughout the study, the abdominal sonar showed only a chronic parenchymatous liver disease, without focal lesions, portal hypertension or ascites.

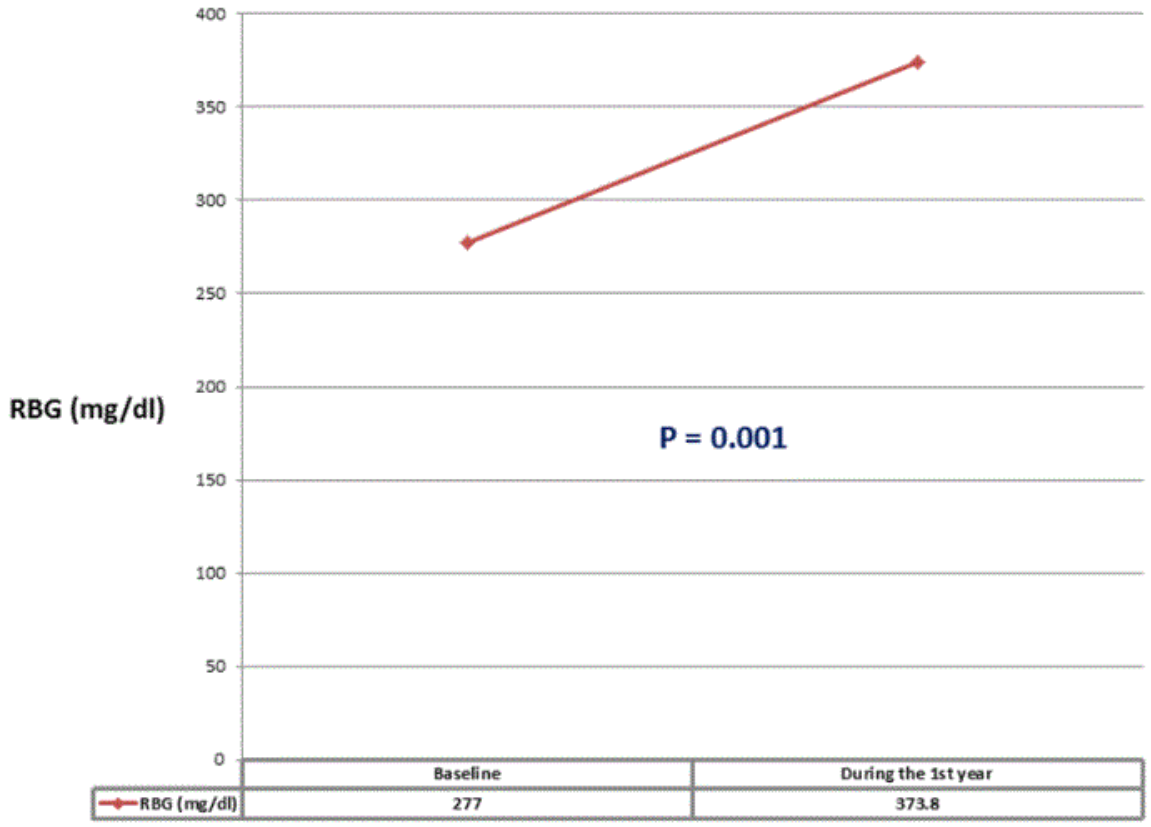


Figure 2: Changes in the random blood glucose (RBG) during the first year of the honey intervention in the twenty patient volunteers with type 2 diabetes mellitus.

Measurement	Value
Age (yr)	55
Weight (kg)	71
Height (cm)	163
BMI	26.7
SBP (mmHg)	170
DBP (mmHg)	85
Hb (g/dl)	12.2
TLC (/mm^3)	7600

Platelets (/mm^3)	220000
ALT (U/L)	65
AST (U/L)	45
Alkaline phosphatase (U/L)	58
Serum bilirubin (mg/dl)	
Total	0.9
Direct	0.6
Serum albumin (g/dl)	4.3
PT	14.5 sec
INR	1.4
Serum creatinine (mg/dl)	0.6
Serum uric acid (mg/dl)	4
FBG (mg/dl)	111
PCR - HCV (IU/ml)	679000

Table 3: Baseline characteristics of the patient, AA, with chronic hepatitis C. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TLC: total leucocytic count; ALT: alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; FBG: fasting blood glucose; PCR-HCV: polymerase chain reaction of hepatitis C virus.

Comparing the blood glucose changes in the 20 patients during the first year of the study found that the mean (±SD) RBG during the first 6 mo. was 351.6 (±90. 56), compared to 404.5 (±88.3) mg/dl during the last 6 months. This difference was statistically significant ($p = 0.0095$). Nine patients (45%) had their RBG frequently rose above 500 mg/dl during the study period. All the patients developed polyuria and polydipsia especially during the first few months of the study, but the daily urine output and water intake were not monitored. The polyuria was sometimes severe. The increased frequency of urination was sometimes associated with urinary urgency, as the patients frequently reported, However, by the end of the first year, the patients reported significant decrease in the severity of polyuria and thirst, and thereafter the severity fluctuated, being increased during periods of stress such as respiratory tract infections. Unexpectedly, these high levels of blood glucose were not associated with dehydration, ketoacidosis or even ketones or albumin in urine. Serum osmolality measured in four patients at levels of blood glucose of 410, 480, 500, and 610 mg/dl, found 274.8, 285, 285, and 290 mOsm/kg; respectively. All the patients who completed one year-clinical trial were able to fast Ramadan months without developing dehydration. Fasting during the Muslim month of Ramadan involves abstinence from food and water for twelve hours or more during the day from dawn to dusk. Especially during the periods of polyuria, the patients drank large amounts of water. They were instructed not to reduce water intake being misled by increased frequency of urination.

Measure	August 2008 to March 2012	April 2012 to April 2014
Body weight (kg)		
Range	67 - 71	65 - 67
Mean ± SD	70.1 ± 2.6	66.2 ± 0.8
SBP (mmHg)		
Range	140 - 170	130 - 160
Mean ± SD	148.4 ± 9.8	140.7 ± 7.7
DBP (mmHg)		
Range	80 - 85	75 - 80
Mean ± SD	80.5 ± 1.5	79.3 ± 1.7

Hb (g/dl)		
Range	12 - 14.2	12.8 - 14.2
Mean ± SD	13.1 ± 0.9	13.2 ± 0.6
TLC (10^3/mm^3)		
Range	5.7 - 7.01	6.3 - 6.7
Mean±SD	6.4 ± 0.5	6.4 ± 0.2
Platelets (x 10^3/mm^3)		
Range	193 - 241	193 - 223
Mean ± SD	207 ± 17.8	205.7 ± 15.5
ALT (U/L)		
Range	57 - 66	43 - 57
Mean ± SD	61.3 ± 3.4	47 ± 8.7
AST (U/L)		
Range	45 - 68	43 - 45
Mean ± SD	55.8 ± 7.5	44 ± 1
Gamma GGT		
Range	166 - 376	185 - 198
Mean ± SD	266.3 ± 88.6	191 ± 6.1
Total serum bilirubin		
Range	0.5 - 0.92	0.92 - 1.18
Mean ± SD	0.72 ± 0.18	1.05 ± 0.18
Direct serum bilirubin		
Range	0.14 - 0.45	0.45 - 0.67
Mean ± SD	0.28 ± 0.14	0.56 ± 0.16
Serum albumin (g/dl)		
Range	4.2 - 4.5	4 - 4.2
Mean ± SD	4.32 ± 0.12	4.13 ± 0.11
PT (seconds)		
Range	11.4 - 16.1	11.4 - 12.1
Mean ± SD	13.97 ± 1.5	11.7 ± 0.35
INR		
Range	1.06 - 1.5	1.06 - 1.18
Mean ± SD	1.28 ± 0.16	1.11 ± 0.06
α-Fetoprotein (ng/ml)		
Range	18.8 - 26.8	12.5 - 22.7
Mean ± SD	22.3 ± 3.1	17.5 ± 5.1

Serum creatinine (mg/dl)	1	0.4
BUN	ND	7
Serum uric acid (mg/dl)	ND	3.8
PCR-HCV (IU/ml)		
Range	26000 - 169000	92059
Median (IQR)	37900 (143000)	

Table 4: Changes in the characteristic values of the patient with chronic hepatitis C during the study period. SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; PT: Prothrombin time; BUN: blood urea nitrogen; PCR = HCV: polymerase chain reaction of hepatitis C virus.

Measure	Date				
	3/012	6/012	10/012	4/013	12/013
FBG (mg/dl)	285	260	257	150.3 ± 1.5	194
PBG	383	350	319	215.5 ± 43.1	282
TC (mg/dl)	118	139		148	
TG(mg/dl)	129	109		99	144
LDL (mg/dl)	60	83		92	50
HDL (mg/dl)	33	38		48	42
VLDL (mg/dl)	26	18		8	28
Apo A-1 (g/L)				1.22	1.25
Apo B (g/L)				0.74	0.7
Hb A1c (%)		10.4		8.1 ± 0.7	
Urine albumin/ creatinine ratio		13.89		15.38	143.75
FCP (ng/ml)		1.5			
PCP (ng/ml)		3.9			

Table 5: The changes in the diabetic status in the patient, AA, with chronic hepatitis C. FBG: fasting blood glucose; PBG: postprandial blood glucose; TC: total cholesterol; TG: triglycerides; LDL: low density lipoproteins; HDL: high density lipoproteins; VLDL: very low density lipoproteins; FCP: fasting C-peptide; PCP: postprandial C-peptide.

Apart from polyuria, polydipsia and loss of weight, no patient developed any of the other clinical manifestations of DKA or HHS. These warning manifestations are dry skin or dry tongue, fruity breath, somnolence, confusion, dyspnea, tachycardia, abdominal pain or vomiting.

In the 10 patients who continued the intervention for more than one year (median=2.6 years), the RBG values ranged from 260 to 610 with a mean (±SD) of 422.40 (±101. 98) at the end of the intervention, compared to 210 to 400 mg and a mean (±SD) of 283.20 (±68. 59) mg/dl at the baseline (p = 0.0075) (Figure 3).

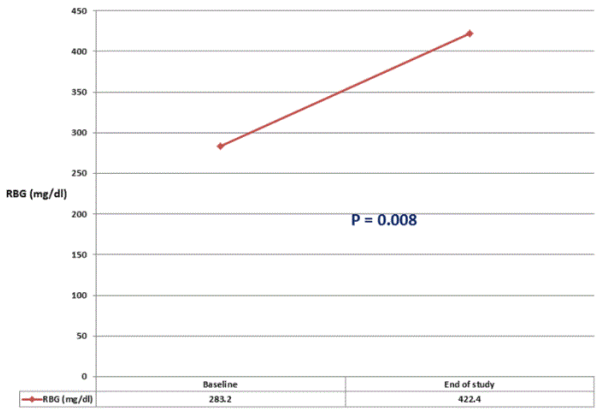


Figure 3: Changes in the random blood glucose (RBG) throughout the period of the honey intervention in the ten patient volunteers with type 2 diabetes mellitus, who continued the intervention for more than one year (median = 2.6 years).

While the fasting blood glucose (FBG) values were statistically significantly higher at the end of the intervention compared to the baseline [287.80 (±98.42) vs. 188.40 (±47.46) mg/dl, respectively; p = 0.0269], there was no statistically significant difference in the post-prandial blood glucose (PBG) values between the baseline and the end of the intervention [320.80 (±65.18) vs. 371.70 (±81.53), respectively; p = 0.1779] (Figure 4). Also, the mean values of RBG did not differ significantly between the end of the first year and the end of the study (395.40 ± 50.48 vs. 422.40 ± 101.98, respectively; p = 0.4035) (Figure 5).

Two female patients, FH and RS, stopped taking honey after intervention periods of 5 months and 2.6 years, respectively, because of persistent hyperglycemia. In addition, they did not also receive anti-diabetic medications. After 1 and 4 months, respectively, the two patients developed DKA and were admitted to the hospital for management. They remained in the hospital for 3 and 7 days, respectively, and discharged improved. After hospital discharge, the first patient stopped the prescribed medicines and resumed the honey therapy, whereas the second patient did not receive honey and resumed her medicines, including insulin.

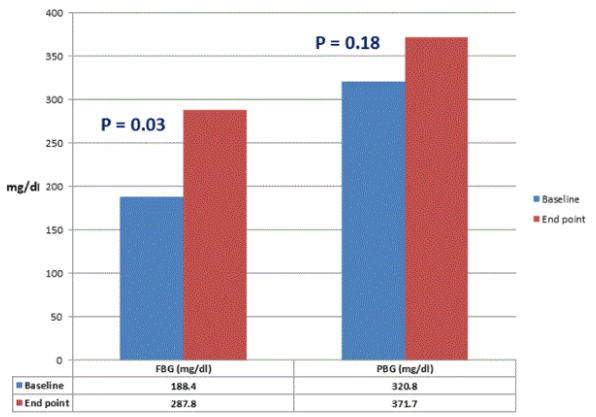


Figure 4: Fasting blood glucose (FBG) and postprandial blood glucose (PBG) after a median honey intervention period of 2.6 years in the ten patient volunteers with type 2 diabetes mellitus, who continued the intervention for more than one year.

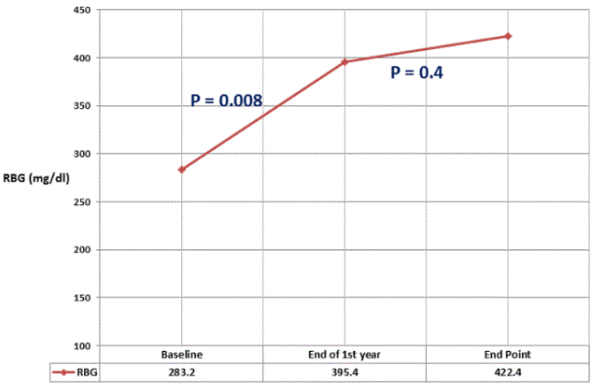


Figure 5: Changes in the random blood glucose (RBG) from baseline to the end of the first year of the honey intervention; and from the end of the first year of the intervention to the end point of the study in the ten patient volunteers with type 2 diabetes mellitus, who continued the intervention for a median of 2.6 years.

Observed in this clinical trial is the rapid drop of blood glucose when the insulin or the hypoglycemic drugs are resumed in the same dosage as before the honey intervention. Some of these patient volunteers even developed hypoglycemia. When the patient, SS, was admitted to the hospital for big toe amputation, he developed hypoglycemia when insulin was given in a dose calculated for correcting his high blood glucose. The second patient, RH, continued the honey intervention for almost 4 years, but when she resumed the insulin in a high blood glucose correction dose, she also developed hypoglycemia. The third patient, FH, continued the honey intervention for 5 months, then she stopped the honey and did not also receive the anti-diabetic therapy. One month later, she developed diabetic ketoacidosis and admitted to the hospital for 3 days. During her hospital stay, her blood glucose also dropped rapidly when insulin was given in a high blood glucose correction dose. The fourth patient, KA, who continued the honey intervention for 1 year, also developed hypoglycemia, when she resumed her oral hypoglycemic drugs in a dose same as before starting the honey intervention. For this reason, author used to instruct the patients, who are intending to stop the honey and resume their anti-diabetic medicines to resume the medicine in a smaller dose, compared with that before the honey therapy.

Body weight changes

All the patients lost weight during the period of the honey intervention. During the first year of the study, the % of weight loss ranged from 1 to 30.3%, with a mean (±SD) of 12.7 % (±6.5). The mean (±SD) body mass index (BMI) at the end of the first year was 28.2 (±6.6) compared to 32.6 (±6.7) before the honey therapy; with a highly statistically significant difference ($p = 0.0001$) (Figure 6). No patient had his or her BMI dropped below 20 by the end of the first year.

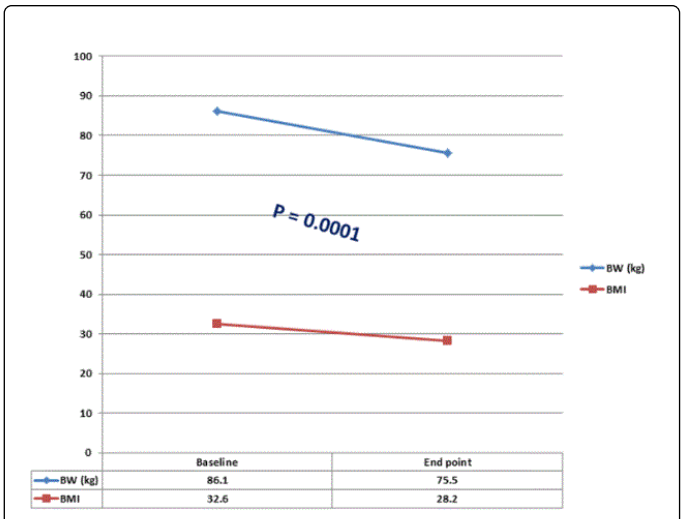


Figure 6: Body weight (BW) (kg) and body mass index (BMI) changes during the first year of the honey intervention in the twenty patient volunteers with type 2 diabetes mellitus.

Even though in AE, a male patient, who had a normal BMI (=23.7) before the study, the BMI dropped to 21.8 after an intervention period of 6 months. Also, all the patients, except one, who continued the intervention for more than one year; the BMI did not drop below 20. However, one patient, RS, had her BMI decreased from 28 to 16.9 after a 2.6-year intervention. Analysis of the results of the 10 patients, who continued the intervention for more than 1 year found the mean (±SD) BMI at the end of intervention became 24.24 (±3.76) compared to 30.8 (±3.5) at baseline ($p = 0.0007$) (Figure 7). Also, it was observed that the rate of weight loss was proportionate to the degree of polyuria.

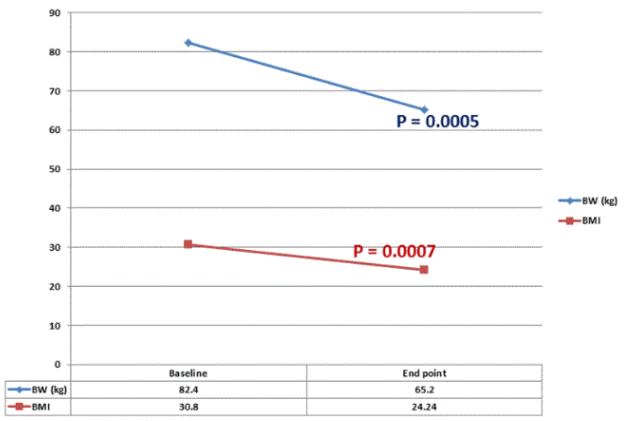


Figure 7: Body weight (BW) (kg) and body mass index (BMI) before and after a median intervention period of 2.6 years in the ten patient volunteers with type 2 diabetes mellitus, who continued the intervention for more than one year.

Blood pressure changes

In the 12 patients who had hypertension at the baseline, the blood pressure decreased and started to approach normal levels about 6 months after the start of the intervention. Comparing the changes in the blood pressure during the first and last 6 months of the first year of the intervention, found the mean (±SD) systolic blood pressure (SBP) during the last 6 months was 125.9 (±12. 6), compared to 141.2 (±13. 97) mm Hg during the first 6 months (P = 0.0003), and the mean (±SD) diastolic blood pressure (DBP) during the last 6 months was 80.02 (±3.2), compared to 88.4 (±4.4) mm Hg during the first 6 months (p = 0. 0001) (Figure 8).

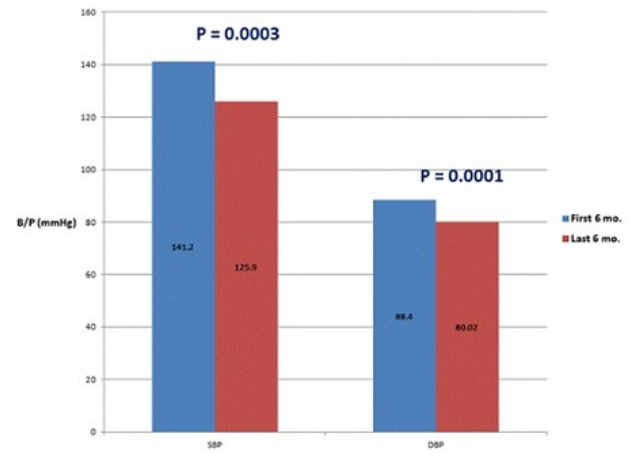


Figure 8: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes during the first and last 6 months of the first year of the honey intervention in the twelve patient volunteers with type 2 diabetes mellitus and hypertension.

In the 6 hypertensive patients, who continued the intervention for more than 1 year (a median intervention period of 4.3 years); the blood pressure remained within the normal levels throughout the remaining period of the intervention (Figure 9).

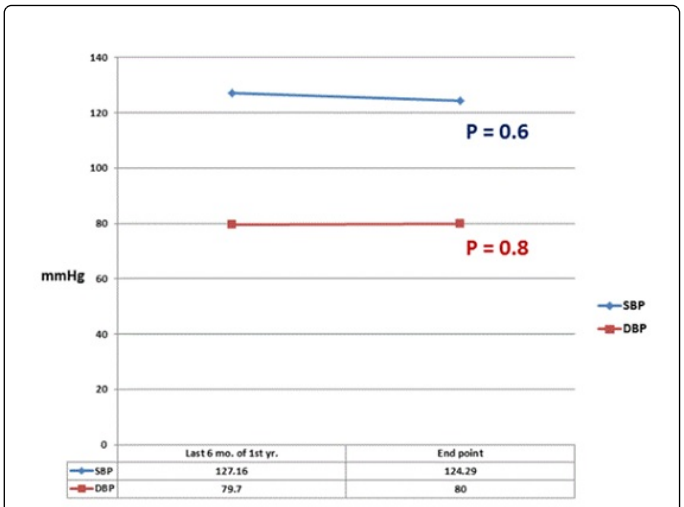


Figure 9: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes during the interval period from the last 6 months of the first year and the end point of the honey intervention in the six patient volunteers with type 2 diabetes mellitus and hypertension, who continued the intervention for a median of 4.3 years.

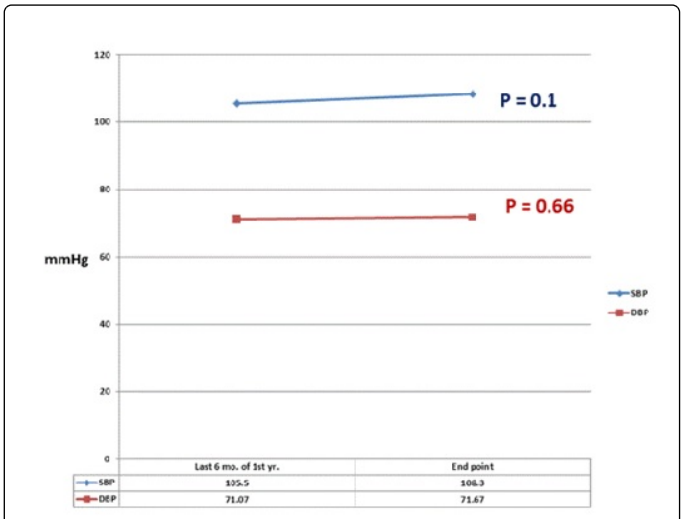


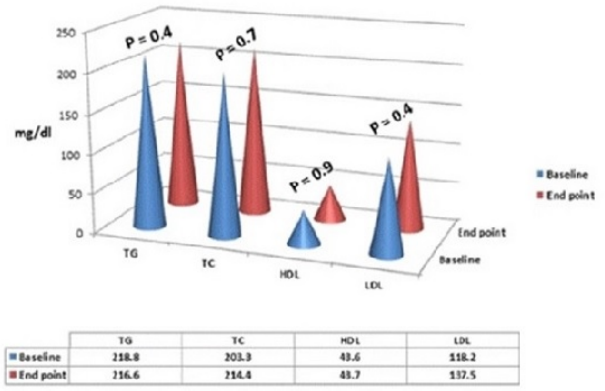
Figure 10: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes during the interval period from the last 6 months of the first year and the end point of the honey intervention in the four patient volunteers with type 2 diabetes mellitus and normal blood pressure (B/P), who continued the intervention for a mean of 2.2 years.

However, after the first year of the intervention, transient elevation of blood pressure to ~160/90 was recorded once or twice yearly in three patients. These episodes of hypertension lasted 2 to 3 days and then resolved without anti-hypertensive medications. On the other

hand, the 8 patients, who had normal blood pressure before starting honey, remained normotensive throughout the period of the honey intervention without significant changes in the levels of blood pressure ($p > 0.05$) (Figure 10).

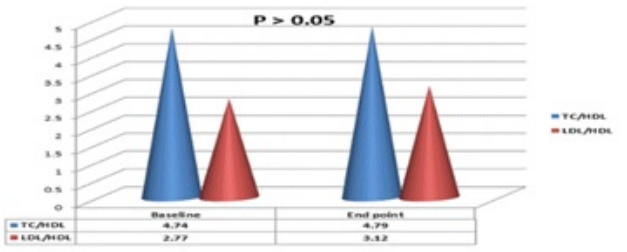
Serum lipid changes

The period of the intervention in the 12 patients, who had dyslipidemia ranged from 0.42 to 13.5 years, with a median (IQR) of 2.2 (3.95) years. At the end of the intervention, the serum lipid profile, including triglycerides (TG), total cholesterol (TC), Low-Density Lipoprotein (LDL) cholesterol and High-Density Lipoprotein (HDL) cholesterol did not show significant changes from the baseline values ($p > 0.05$) (Figure 11).



	TG	TC	HDL	LDL
Baseline	218.8	203.3	48.6	118.2
End point	216.6	214.4	48.7	137.5

Figure 11: Serum lipids; triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), and low density lipoprotein (LDL) before and after a median intervention period of 2.2 years in the twelve patient volunteers with type 2 diabetes mellitus and dyslipidemia.



	Baseline	End point
TC/HDL	4.74	4.79
LDL/HDL	2.77	3.12

Figure 12: Serum lipid ratios [total cholesterol (TC)/ high density lipoprotein (HDL), and low density lipoprotein (LDL)/ high density lipoprotein (HDL) ratios] before and after a median intervention period of 2.2 years in the twelve patient volunteers with type 2 diabetes mellitus and dyslipidemia.

Also, analysis of the results of the 10 patients, who continued the intervention for ≥1 year found no significant changes in the serum lipid values between the baseline and the end of the intervention ($p > 0.05$). The TC/HDL and LDL/HDL ratios did not also show significant changes between the baseline and the end of the intervention ($p > 0.05$) (Figure 12). However, measurements of Apo-lipoprotein (Apo) A-1 and Apo B in the two patients, SS and MA, who completed until today 13.5 and 9.3-year intervention, respectively, found a normal Apo A-1 level after periods of intervention of 10 and 7 years, respectively.

Cardiovascular status

No one of the patient volunteers showed any deterioration of his/her cardiac condition during the period of the honey intervention. Moreover, the four patients with CHD at the baseline, had had their cardiac condition improved, as shown by improved exercise tolerance, absence, or at least decreased frequency and duration, of angina or angina-like pains, absence of ECG changes of myocardial ischemia, and improved left ventricular function and ejection fraction, as shown in the Doppler Echocardiography. The first patient, RH, had a history of type 2 diabetes and CHD of 7 years duration. During this period, she was admitted to the cardiac intensive care unit with acute myocardial ischemia more than one time. In January, 2005, she participated in the study and continued the honey intervention for almost 4 years. During this period of honey intervention, her cardiac condition improved and remained stable, as shown by the improvement of the exercise tolerance and the absence of true angina pains. However, she stopped the honey therapy and resumed her medicines, including insulin because of the persistent hyperglycemia and weight loss. Three years after discontinuation of the honey intervention, her cardiac condition started to deteriorate; her myocardial perfusion study showed deterioration of overall left ventricular function. The global left ventricular ejection fraction decreased to 28%. At this time, she started to receive honey along with her medicines for one year, until 2013, then she stopped the honey and continued her medicines until today. Only the data of this patient's 4-years honey intervention, without medicines were included in the final analysis. The second patient, HA, had coronary heart disease and retinal hemorrhage due to proliferative diabetic retinopathy. He stopped his medicines and started the honey therapy on 31 March, 2002. He continued the honey intervention from 31 March, 2002 until 19 November, 2002; then he stopped the honey and resumed his medicines because of the persistent hyperglycemia. During this 7.5 months- honey intervention, his cardiac condition was stable and his eyes showed improvement by about 20%, as reported by the ophthalmologist. However, 3 months after the stoppage of honey, on 4 March, 2003, he developed acute chest pain, and was admitted to the intensive care with the diagnosis of non- ST segment myocardial infarction, because his ECG was normal, but the cardiac enzyme CK-MB was elevated (32 U/L). He was discharged improved from the hospital after 2 days, and thereafter, he continued his medicines without honey. The third patient, TA, continued the honey intervention for 6 years. Thereafter, he stopped the honey and resumed the anti-diabetic medicines because of the persistent hyperglycemia and loss of weight. Six months before the stoppage of honey, clinical examination and investigations showed: normal heart and chest examination, normal blood pressure (120/80), normal fundus, BMI of 20.1, FBG of 303 mg/dl, HbA1C of 14%, normal renal functions (serum creatinine of 0.97 mg/dl, and blood urea of 12.9 mg/dl), dyslipidemia (TG = 122, TC = 245, HDL = 56, LDL = 152 mg/dl), normal ECG (sinus rhythm, HR = 86/min, no abnormal axis deviation, no abnormal T-wave inversion, no ST segment depression or elevation, and no pathologic Q wave), and normal Doppler Echocardiography. However, three years after the discontinuation of honey, he again developed hypertension, cardiac dysfunction, peripheral neuropathy,

retinopathy and renal failure. The fourth patient, SS, started to suffer coronary insufficiency when he was 40 years old. At the age of 43, implantation of stents for his right coronary and circumflex arteries was done. In addition, he has a strong family history of CHD; his father and elder brother died of CHD in the fiftieth, and his younger brothers had also CHD. In 2002, when he was 45 years old, he participated in this clinical trial and continued the honey intervention until today. Throughout this 13.5-years honey intervention, his cardiac condition remained stable, with normal ECGs. Also, his Doppler Echocardiography, done every year, did not show segmental wall motion abnormalities, and his ejection fraction remained within the normal range.

Cerebral strokes

During the period of the honey intervention, no patient developed cerebral strokes. However, two patients, TA and SS, who continued the honey intervention for 6 and 13.5 years, respectively, reported non focal transient neurologic attacks one to three times every year. During these attacks, the two patients developed only dizziness for only a few seconds. These attacks were not transient ischemic attacks because the patients did not develop weakness, numbness or paresis in the face, arm or leg. Also, they did not develop confusion or trouble speaking or understanding speech, or any visual disturbance. Further, they did not develop any loss of balance or coordination. For these reasons, no action was taken. It should also be mentioned that the two patients reported that they had more frequent similar attacks before the honey intervention.

Renal functions and Micro-albuminuria

During the period of the honey intervention, the renal functions in the form of serum creatinine and blood urea remained normal in all the patient volunteers. However, screening for the micro-albuminuria was done for 5 patients; three of them (RS; MA; and SS) showed micro-albuminuria after 2.6, 7.25 and 10.6- year intervention with levels of 427.2, 31.8 and 43.2 mg albumin/g creatinine, respectively. In MA, a test for micro-albuminuria done on 2 July, 2015 after 8.5 years-honey intervention, showed a normal result; it decreased from 31.8 to 13.2 mg albumin/g creatinine. In SS, who continued the honey intervention until today (almost 14 years), the microalbuminurea increased from 43.2 in March 2013 to 64.98 in March 2014; then decreased to 55.6 in March 2015 [normal levels <30 mg albumin/g creatinine]. On the other hand, the patient, RS, stopped the intervention after 2.6 years; then she lost to follow-up. One patient, TA, had normal renal functions throughout his 6 years honey intervention period, but 3 years after the discontinuation of the honey therapy, he developed renal failure.

Eye problems

Two patients developed eye problems after almost an 8-year honey intervention. The first patient, SS, developed a non-proliferative retinopathy, and the second patient, MA, developed cataract. In the first patient, regular fundus examination every 6 months during the last 6 years did not show progression of the retinopathy. Surgery for the cataract was done last year in the second patient.

Peripheral neuropathy

At the baseline, before the honey intervention, 12 (60%) of the 20 patient volunteers had peripheral neuropathy, manifested as numbness, tingling, and sometimes pain mainly in the lower limbs. In these patients, the neuropathy did not worsen during the period of the honey intervention, but however, in one patient, SS, who continued the intervention for almost 14 years, the clinical picture of neuropathy progressed to weakness and wasting of the lower limbs after 8-years honey intervention, and he developed a diabetic foot. In the same patient and during the last 6 years, the weakness and wasting did change, but the severity of symptoms was fluctuating.

Before the honey intervention, 9 (75%) of the 12 male volunteers, complained of erectile dysfunction, and they did not report improvement with the honey therapy.

Infections

No patient developed any serious infection like malignant external otitis, rhino-cerebral mucormycosis and gangrenous cholecystitis, to which the patients with DM are especially vulnerable.

Also, although no patient received anti-pneumococcal or anti-influenza vaccine; the frequency, and the duration and severity of the upper respiratory tract infections decreased as reported by the patients. However, one patient, SS, developed a diabetic foot after an 8-year honey intervention. More than one vascular surgeon recommended below knee amputation, but the patient refused, and amputation of the big toe only was done. In this patient, although the wound infection was severe, he did not develop DKA or HHS, and with topical honey without antibiotics complete healing of the wounds occurred. The process of healing of the wounds, including the surgical ones was slow; it lasted about 2 years.

Discussion

Magnitude of the problem

Diabetes mellitus is the most common metabolic disorder in all countries including Egypt. The complications of DM are responsible for not only significant morbidity and mortality, but also for a large economic burden. In the USA, for example, the estimated total economic cost of diabetes in 2012 was $ 245 billion.

Justification of the research

The author tried in this clinical trial to test the effects of honey, as an alternative, natural and non-expensive substance in the treatment of DM and its complications, based on the preliminary results obtained in some patient volunteers, who stopped their drugs and used honey in large doses, as a sole treatment of their diabetes and its associated metabolic disorders. In the face of the persistent honey-induced hyperglycemia, the body weight of these patients decreased without diet restrictions, and they did not develop DKA or HHS. The anti-oxidant [12-14], the anti-microbial [15-19], the immune modulator [20] and the anti-inflammatory properties [21-24] of honey helps also justification for this research.

The current management of DM failed to cure diabetes or to completely prevent its complications. The acute complications of diabetes; DKA and HHS, still happen. Also, although intensive control of glycemia might decrease the micro-vascular complications, it may be associated with an increased risk of mortality not only from the increased incidence of hypoglycemia, but also from the increased risk of macro-vascular complications particularly CHD [2-4]. Further, drugs used in the treatment of DM and its complications have many

side effects, including the hypoglycemia, which is not related to the disease per se, but related to the hypoglycemic drugs.

Scientific evidence supporting the use of honey as a sole treatment of diabetes does not exist. In this clinical trial, the patient volunteers stopped their medicines and took honey as an alternative treatment. This is a potentially risky trial; these patients might be liable to the complications of hyperglycemia, and might also be harmed of the sequelae of uncontrolled hypertension, dyslipidemia and coronary insufficiency. On the other hand, the current management of DM also carries risks; the hypoglycemia, the failure of medicines to prevent the complications, and the side effects of drugs.

Honey as a sole treatment of type 2 DM: Sequence of events

The effects of honey as a sole treatment of type 2 DM were discovered by chance. Many *in vitro* and animal studies and a few human studies have demonstrated that honey has powerful healing effects, especially as an anti-microbial agent and as a wound healer. However, author did not think of giving honey to patients with diabetes because of its high sugar content.

At the beginning, the possibility of terminating this study within a few days was high. As expected, all the patients developed more hyperglycemia as a result of the honey intervention, but, unexpectedly, the rise of blood glucose levels, which frequently exceeded 500 mg/dl, did not lead to dehydration, acidosis or even ketonuria in any of the patient volunteers. These initial findings encouraged me and the patient volunteers to continue the trial despite the potential risks still existed with this worrysome hyperglycemia.

With this persistent hyperglycemia, all the patients developed polyuria, polydipsia, and loss of weight. Further, the blood pressure in the hypertensive patients started to decrease and to approach the normal levels, whereas in the normotensive patients, the blood pressure remained normal. Also, the patients with CHD showed improvement in the exercise tolerance, as they reported. Moreover, no patient developed a cerebral stroke.

Inspite of these positive effects the possibility that this persistent hyperglycemia might lead to complications at any time still existed.

Only because of the persistent hyperglycemia, the majority of the patient volunteers stopped the honey therapy after sometime, and resumed their medicines, whereas a few patients continued the study waiting for possible glycemic control.

The two patients, MA and SS, accepted this persistent hyperglycemia until now for almost 9 and 14 years, respectively, despite the first developed cataract and the second developed peripheral neuropathy and a diabetic foot, which resulted in amputation of his big toe.

The honey intervention resulted in all the patients in persistent hyperglycemia, and in persistent dyslipidemia in the patients, who had disturbed lipid profile at the baseline. Unexpectedly, this persistent hyperglycemia and dyslipidemia did not lead to the development of any of the macro-vascular complications; CHD, hypertension or cerebral stroke, in the patients who did not have any of these complications before the trial. On the contrary, the blood pressure became normal and the cardiovascular status improved in the patients, who had hypertension or a CHD before the study. These unexpected positive effects might be due to weight reduction or the anti-oxidant effects of honey; or both. In vitro and animal studies have demonstrated that honey reduced the oxidative stress in diabetes [13,27-29], a factor contributing to vascular dysfunction. The effects of the honey to reduce the vascular reactive oxygen species and to increase the bioavailability of nitric oxide [13,29-31] might be the mechanism underlying the positive effects of honey in reducing or preventing the deterioration of the vascular endothelial function, and hence the macro-vascular complications, in these patients.

The observed positive effects on the macro-vascular complications are probably due to honey, and do not represent a natural course of the patient's disease. This is because discontinuation of honey resulted in DKA in the two patients, who stopped the honey after intervention periods of 5 months and 2.6 years, without resuming their anti-diabetic medications. Also, discontinuation of honey resulted in deterioration of the cardiac condition in the patient, R. Hammad, who had already a CHD, and in whom the cardiac condition has remained stable throughout the 4-year honey intervention. Further, the blood pressure improved and the cardiac condition has been stabilized throughout the 6-year honey intervention in the patient, T. Alobaid, who had hypertension and CHD before starting honey, but 3 years after the discontinuation of honey he again developed hypertension and cardiac weakness.

Another unexpected positive finding is that the persistently high levels of blood glucose did not lead to DKA or HHS particularly during periods of stress and during the fasting month of Ramadan. It seems likely that the honey prevented these life-threatening events in the face of the high levels of blood glucose. A supporting finding to this hypothesis is the development of DKA in the two patients, who did not take any hypoglycemic drug after the discontinuation of the honey intervention. The most common cause precipitating DKA or HHS is an infection [32-35]. The anti-microbial properties of honey [18] might thus be one of the main factors, which protected against DKA and HHS. However, mechanisms other than the anti-microbial mechanism, by which the honey prevented these complications, may also exist, because during the present study, the patients also acquired infections, but they did not develop either DKA or HHS. A possible mechanism is the anti-oxidant effect of honey, which might prevent the oxidation of free fatty acids in the liver to ketone bodies [32]. In HHS, severe osmotic diuresis may lead to dehydration without ketosis. In all the patients with marked hyperglycemia and in whom the serum osmolality was measured, the effective serum osmolality did not exceed the upper normal value of 290 mOsm/kg. However, the serum osmolality was not regularly measured in all the patient volunteers. The patient' ability to drink a large amount of water during the periods of polyuria might contribute to the prevention of HHS. Based also on the equation: the effective serum osmolality = 2 [measured Na^+ (mEq/l)] + glucose(mg/dl)/18 [32], it might be hypothesized that honey, by modulating the levels of serum sodium and glucose, helped prevention of the effective serum osmolality from reaching levels more than 290 mOsm/kg; i.e., when the glucose level increases, the serum sodium might decrease.

There is a general agreement that glycemic control is needed to reduce the complications from diabetes, but there is still a controversy about the levels of blood glucose optimal to achieve this goal. Despite intensive control of glycemia might decrease the micro-vascular complications, no marked effects have been reported on the macro-vascular complications or all-cause mortality. Moreover, intensive glycemic control may be associated with an increased risk of mortality [36]. Furthermore, intermittent hyperglycemia (glucose spikes), as compared to persistent hyperglycemia, induces apoptosis of vascular endothelial cells [37]. Also, considerable data have accumulated

indicating that elevated Postprandial Glucose (PPG) levels, even in the absence of high Fasting Blood Glucose (FBG), increase the risk for Cardiovascular Disease (CVD) [38,39]. Therefore, besides controlling overall glycemia, reduction of PPG and adjusting the fluctuations of blood glucose might also be needed to prevent or treat CVD. However, achieving such an "ideal" glycemic control using only the conventional anti-diabetic medicines may be faced by the hypoglycemia as a major risk obstacle. Previous studies have shown that honey has an attenuated postprandial glycemic response [27,28,40-43]. In the present study, the levels of PPG did no show significant difference before and after the honey intervention in the 10 patients, who continued the intervention for a median of 2.6 years (range = 1.08 - 13.5 years). Therefore, the positive effects of honey on PPG and the possibility that honey intake prevented glucose spikes might explain why the macro-vascular complications are reduced in these patients in spite of persistently high HbA1C. Thus, the PPG and the glucose spikes might be more important predictors of the major cardiovascular events than the HbA1C. Based on these observations, the following questions might be addressed: First, what would be the ideal PPG level in patients with type 2 diabetes; is it an ideal level per se [44] or an ideal FBG/PPG ratio? Second, what would be the ideal range of blood glucose fluctuations or spikes below which no major cardiovascular events would be predicted? Future studies might answer these questions.

In the patients with hypertension, honey intervention resulted in lowering of blood pressure to <140 mmHg systolic and <80 mmHg diastolic. Randomized clinical trials have demonstrated the vascular benefit of lowering blood pressure to these levels in individuals with diabetes [45]. Thus the beneficial effect of honey on B/P might also be a contributing factor in preventing strokes and reducing the major cardiovascular events in these patients.

Although the serum levels of TC, TG, LDL and HDL did not show significant change before and after the honey intervention in the patients with dyslipidemia, the major cardiovascular events are reduced. This observation further supports the recommendation of considering the routine measurement of other lipids in the patients with diabetes [46]. Other studies also support this recommendation because the risk of major cardiovascular events remained in the range of 20% after 3 years of follow-up after an acute coronary syndrome in spite of lowering of LDL cholesterol using statins [47]. Moreover, measurement of LDL cholesterol may not accurately reflect the true burden of atherogenic small LDL particles [48]. Also a measurement of HDL cholesterol alone may not accurately reflect the anti-atherogenic capacity of HDL [49]. It has been suggested that Apo B and Apo A-1 may not only be relevant predictors of CHD [50], but also may provide more accurate information than LDL and HDL [51]. In this study, the abnormal serum lipid profiles persisted throughout the study period. However, measurements of Apo A-1 done in only two cases found it normal after 7 and 10-year honey intervention, respectively. ApoA-1 plays a critical role in preventing and reducing astherogensis [52-54]. Therefore the preservation of Apo A-1 might also be a possible mechanism by which honey reduced major cardiovascular events. It might also be suggested that honey might have inhibited the formation of oxidized LDL [28], or might have reduced the burden of atherogenic small LDL particles, which were not measured in our study; or both.

Honey intervention also resulted in a significant weight loss in all the patients. In the 10 patients, who continued the intervention for more than 1 year, the mean (±SD) BMI at the end of intervention became 24.24 (±3.76) compared to 30.8 (±3.5) at baseline ($p = 0.0007$). Weight reduction might be considered as an important factor contributing to the reduction of the macro-vascular complications in these patients.

To summarize; the possible mechanisms underlying the beneficial effects of honey on the macro-vascular complications of DM in these patients include; weight reduction, lowering of blood pressure in hypertensive patients, attenuation of postprandial hyperglycemia and preservation of Apo A-1. However, other potential mechanisms that need documentation include the effects of honey on glucose spikes and atherogenic small LDL particles, which may need further studies.

Further, the observation that some of the patient volunteers developed hypoglycemia, when they stopped the honey and resumed their anti-diabetic medicines in a high blood glucose correction dose, may show, on clinical grounds, that honey might have the potential to heal the pancreatic insult and to improve the insulin resistance.

With the honey intervention, some of the micro-vascular complications of DM developed in the two patients, SS and MA, after almost an 8-year honey intervention. In the first patient, SS, the peripheral neuropathy increased, and he developed a diabetic foot. He also developed a non-proliferative retinopathy. The second patient, MA, developed cataract. SS and MA are the only patients, who completed 13.5 and 9.3 years-honey intervention until today, respectively. The question: would these complications developed these patients had not been given honey? Longer term follow-up of these two patients might help answering this question. Also, comparing the effects of long term use of honey as a sole treatment of type 2 DM with the current anti-diabetic medications in future studies with large cohorts of patients may help answering this question. Another question: would these micro-vascular complications do not develop these two patients had received anti-diabetic medications concomitantly with honey? Well-designed controlled studies on large groups of patients may be needed to see whether the intake of honey, as a complementary agent, concomitantly with the anti-diabetic medications has the potential to prevent, cure or reduce both the macro-and micro-vascular complications of diabetes. On the other hand, the peripheral neuropathy did not progress with the honey intervention in the other patients, who had already peripheral neuropathy before the honey intervention. As a limitation to this study, screening for the micro-albuminuria was done for only 5 patients; three of them showed micro-albuminuria after 2.6, 7.25 and 10.6- year honey intervention. However, the micro-albuminuria disappeared one year after the 7.25-year honey intervention in the patient, MA; but it persisted until today in the patient, SS, who continued the intervention for almost 14 years. On the other hand, the renal functions in the form of serum creatinine and BUN remained normal in all the patients throughout the period of the honey intervention, even in the 3 patients, who continued the intervention for 6 years or more.

Most of the infections developed during the honey intervention were upper respiratory tract infections, which, as the patients reported, were less severe, when compared with similar infections before starting honey. In general, patients with diabetes are at increased risk of infections [55], which are usually respiratory tract infections [56]. However, some serious infections usually affect only persons with diabetes, such as malignant external otitis, rhinocerebral mucormycosis, and gangrenous cholecystitis [55]. Although some infections in DM are potentially serious, infections in general may predispose to DKA and HHS. Although the patient volunteers remained with persistent hyperglycemia throughout the duration of the honey intervention, no patient developed any of these serious

infections, or DKA or HHS. Also, the patient, who developed a diabetic foot, did not develop DKA or HHS, despite the wound infection was severe and necessitated amputation of the big toe. Moreover, honey therapy, both orally and topically without antibiotics, resulted in healing of wounds in this patient. These findings further support the evidence that honey has anti-microbial effects [18].

Honey is not a simple mixture of sugars and water, as some believe. It is a complex product containing many other substances, including trace elements, acids, vitamins, enzymes, and phenolic compounds [26]. Also, honey contains unknown compounds, and new analytic procedures are developing to identify these compounds [57]. Honey is not simply a food with a medicinal value, but primarily a medicine, which has a nutritive value. There are many references to honey as a medicine in ancient scrolls, tablets and books. It was prescribed for a variety of illnesses. In ancient Egyptian medicine, honey was the most frequent ingredient in all the drug recipes for both internal and external use listed in the Ebers and Edwin Smith Papyri [58]. The constituents of honey probably act in harmony and synergy with one another as one unit to produce its beneficial effects. Honey probably produces healing by direct and indirect effects. The direct healing effects of honey have been demonstrated in wounds [59,60], and the indirect way, by which honey produces healing, is probably due to its immune modulator properties [20]. The pathogenesis of DM and its complications is not completely understood. Also, the mechanisms underlying the healing power of honey in many diseases are not completely understood. The combined anti-oxidant [12-14], anti-microbial [15-19], anti-inflammatory [21-24], prebiotic [10], probiotic [61], and immune modulator [20] effects of honey are probably responsible for the beneficial effects of honey observed in this group of patient volunteers suffering from diabetes and its associated metabolic derangements. However, other hidden mechanisms, by which honey produces healing, probably exist and need further researches.

Literature search did not find clinical trials similar to this study, in which the patients stopped the drugs and used honey as a sole treatment of their illnesses. However, in the study of Bahrami, et al. [62] honey consumption for 8 weeks in patients with type 2 DM resulted in weight reduction and improved lipidemia, but the levels of HbA1C increased. The present study differed from Bahrami and colleagues' study in two main aspects; first; the study of Bahrami, et al. was a randomized controlled study of only 8 week duration. Second; the patients consumed honey with the anti-diabetic medications. The present study, on the other hand, was a cohort study, which involved a group of patient volunteers, who used honey as a sole treatment of DM for a median of 1.09 years. However, the improved lipidemia observed in the study of Bahrami, et al. [62] may again raise the question: would the use of honey concomitantly with the anti-diabetic medications, have the potential to improve the lipid profile, and hence to prevent or reduce both the macro- and micro-vascular complications? This may need well-designed randomized controlled studies in large cohorts of patients to see which is better; to use honey alone or with anti-diabetic medications.

Study interactions and limitations

What was behind the patient's agreement to stop their medicines and participate in this potentially risky trial? Many reasons were behind this; the religious believe that honey is a healing agent, was the main reason. Also, all the patients were seeking for an alternative treatment for a cure; no disease, hence no drugs, and no diet or other restrictions. The religious belief in the healing power of honey is present in Muslim and non-Muslim people. The honey was mentioned in several religious books, including Qur'an, Torah, Bible, Hinduism, and Buddhism. The Quran, the last revealed word of God (ALLAH), is the primary source of every Muslim's faith and practice. It deals with all the subjects which concern human beings. It is widely regarded as the finest piece of literature in the Arabic language. The Quran was revealed to Muhammad in Arabic only. So, any Quranic translation, either in English or any other language, is neither a Quran, nor a version of the Quran, but rather it is only a translation of the meaning of the Quran. The Quran exists only in the Arabic in which it was revealed. Qur'an chapters are called Suras and Verses, Ayahs. An entire Surah in the Qur'an called al-Nahl (the Honey Bee) in which mentioned and your LORD inspired the bees, saying: "Take your habitations in the mountains and in the trees and in what they erect". "Then, eat of all fruits, and follow the ways of your Lord made easy (for you)". There comes forth from their bellies, a drink of varying colors wherein is healing for men. Verily, in this is indeed a sign for people who think deeply" (Surah Al-Nahl). The sentence: "There comes forth from their bellies, a drink of varying colors wherein is healing for men" means the honey, which comes forth from the bellies of bees, is a drink with different colors wherein is healing for men.

Muslims believe, as mentioned in Surah Al-Nahl, that honey, which comes forth from the bees, has a healing effect on diseases affecting man. The religious believe was the main reason behind the patient's agreement to participate in this risky trial. On a scientific basis, it is hard to believe that honey ingestion will not harm the patients of diabetes because of the high carbohydrate content of honey. The author and the patient volunteers thought that honey might have the power of healing diabetes. We meant by healing or cure from diabetes is normalization of blood glucose, remission of all associated metabolic disturbances and improvement of all the complications if present. However, this did not happen during the period of the honey intervention, and because of the persistent hyperglycemia 36 of the 38 (~95%) patients enrolled in the study, stopped the honey intervention and resumed their medicines after sometime. These patients reported either that the honey they consume is not an original honey or that the honey is effective in diseases other than diabetes. The only two patients, who were continuing the honey intervention, without medicines, until today, probably realized that the honey's hyperglycemia without major complications and without diet or drug restrictions is better than the normoglycemia with possible major complications and with diet and drug restrictions.

Before the study, most of the patients had already their diabetes uncontrolled; 16 (80%) of the 20 patients had their HbA1C >8, mainly because of poor compliance with their medicines. With the honey intervention, the blood glucose was not controlled; it increased and reached high worrisome levels. Only because of the persistent hyperglycemia, 18 (47%) of the 38 patients enrolled, discontinued the honey before 3 months. Also, 16 (80%) of the 20 patients, who continued the intervention for more than 3 months, stopped the intervention after sometime and resumed their medicines. The only two patients, SS and MA, who continued the honey intervention, without drugs, until today, probably realized that the control of their blood sugar is not the main factor needed to prevent or cure the life threatening complications of diabetes. The patient, SS, who completed almost 14 years-honey intervention until today, was always afraid of sudden death from CHD as his father and elder brother died of acute myocardial infarction despite they were compliant to their medicines. He did not respond to the psychological stresses from the people around him, including his elder brother, who died in 2007, and despite

he developed a diabetic foot and retinopathy, he continues the intervention until today. He did not usually care about his high blood sugar as long his cardiovascular status remained stabilized. The second patient, MA, completed until today, almost 9 years-honey intervention. She was not bothered by the persistent hyperglycemia; as she usually reported that she is feeling good with honey, without drugs or restrictions. The patient, FH, had had morbid obesity before the study; her BMI was 56. Before the beginning of honey therapy, her body weight was 140 kg, and blood pressure 160/100. After 5 months-honey intervention, her body weight decreased to 132 kg, and her blood pressure to 145/90. She reported that she feels happy as her weight and blood pressure started to decrease, without drugs or diet restrictions. However, when she stopped the honey, and did not receive the anti-diabetic drugs, she developed DKA, as was mentioned before. Thereafter, she resumed the honey therapy, but she was sometimes receiving honey alone, and at other times with the anti-diabetic medications. Therefore, only the data of this patient during the 5 months- honey intervention, without drugs, were included in the final analysis.

Also, the patient, RH, was afraid of hyperglycemia. When her cardiac condition and blood pressure stabilized after 4 years-honey intervention, she stopped the honey and resumed her medicines for 3 years. When her cardiac condition showed deterioration, she resumed the honey therapy with the anti-diabetic medications for one year, but thereafter, she received only the medicines until today. Therefore, only the data of this patient during the 4 years-honey intervention, without medicines, were included in the final analysis.

The patient, TA, continued the honey intervention, without medicines, for almost 6 years. During this period, his blood pressure and cardiac status stabilized, his BMI decreased from 34.5 to 20.1. However, he stopped the honey and resumed his medicines because of persistent hyperglycemia, erectile dysfunction and loss of weight. His weight decreased from 92 kg before the intervention to 54 kg after 6 years.

All the patient volunteers were exposed to psychological stresses from the people around them during the period of the honey intervention because of the uncontrolled blood sugar. Each fatigue or illness suffered by the patient during this period was nearly always attributed to the honey-induced hyperglycemia.

It may be hard to believe, but it is not difficult to confirm the results of this study. The problem of diabetes lies in its complications. A patient with hyperglycemia without drug or diet restrictions and with little or no complications is better than a patient with controlled blood sugar, but on drugs, and with more complications. This honey-induced hyperglycemia was associated with such benefits as weight reduction without diet restrictions, control of blood pressure in the hypertensive patients, improvement of the cardiac condition in the patients, who had CHD. Further, this honey induced hyperglycemia did not lead to a coma. Also, it did not lead to a cerebral stroke or a deterioration of the cardiovascular status. All these unexpected findings, discovered by chance, happened without medications or a specific dietary regimen. However, this does not mean that the hyperglycemia is generally beneficial to the patients of diabetes. However, the hyperglycemia without honey is harmful as it led to DKA in the two patients, who stopped the honey and did not receive anti-diabetic medicines.

Based on the current international guidelines, the only available and suitable treatment of DM and its complications is the use of the current traditional medications, despite side effects and complications. Because there is not yet a better treatment alternative to the current treatment, from the current medical ethical point of view, it is not ethical to stop these medications and use a natural substance with a high caloric content. However, there are some points that should be clarified:

At the beginning author did not plan to use honey, as a sole treatment of DM and its associated metabolic derangements, but the initial unexpected positive effects observed, by chance, when honey was given, encouraged him and the patients to continue the trial waiting for the possible remission of diabetes. When the patients did not develop DKA or HHS despite the worrisome hyperglycemia, and when their body weight decreased, their blood pressure controlled, and their cardiovascular status improved, he thought these unexpected positive results will be followed sooner or later by control of blood glucose and remission of diabetes. However, until today this did not happen as shown in the study. The improvement of the macro-vascular complications in the face of the persistent hyperglycemia and dyslipidemia, and the body weight reduction despite no diet restrictions, supports the fact that the pathogenesis of DM and its complications is not fully understood. Also, it supports the findings of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT) [2-4], which showed no improvement in cardiovascular disease and death with tight glycemic control. Further, it supports the hypothesis that the mechanisms underlying the healing power of honey are not fully understood.

The current medications of DM and its associated metabolic disorders, have failed to produce satisfactory results because the current medications failed to produce remission of the disease. Also, with the current medications, still the complications, especially the macro-vascular complications, occur. Moreover, the current medications of diabetes and its associated metabolic disorders have much side effects, which are sometimes life threatening , such as hypoglycemia, which is a frequent complication not related to the disease per se but to the hypoglycemic agents, cardiac arrhythmias and angioedema due to the anti-hypertensive medications, and statin-triggered autoimmune myopathy, which may be life threatening. Some of these life threatening complications may not be preventable. The question: Is it ethical to prescribe a medicine, which might produce a life threatening complication and death in patients with diabetes provided the benefits of such medicine outweigh the risks? If the answer is yes because there is not yet an alternative, then the results of the present study, which used honey as a sole treatment in a small group of patients with diabetes, warrants further studies in larger groups of patients. If the future studies confirmed the results of the present study, we can then compare the honey with the current medications, as shown in Table 6.

Item	The current medications	Honey
Hyperglycemia	Can be controlled	The hyperglycemia increased, but without DKA or HHS

	If not controlled, the patient may develop DKA or HHS, but if tightly controlled, the patient may develop hypoglycemia	
Hypoglycemia	Not uncommon. The episodes of hypoglycemia may be life threatening	Did not occur
Overweight/obesity	Difficult to achieve weight reduction	Weight reduction achieved without drugs or diet control
Hypertension	Can be controlled under the effect of anti-hypertensive drugs and/or diet control, but in some patients the blood pressure cannot be controlled	Controlled without drugs or diet regimen
Coronary heart disease (CHD)	Can be controlled by angina medications, but the mortality remains high. Invasive procedures like stent or coronary replacement may be done if the drug therapy failed, but recurrence is not uncommon	Improved. All patients who had a CHD remained stable throughout the course of honey therapy without any deterioration of their cardiac status
Cerebral strokes	Not uncommon	Did not occur throughout the course of the honey therapy
Dyslipidemia	May be controlled, but the lipid controlling drugs have many side effects	The lipid levels in the blood remained abnormal throughout the honey therapy, but the ApoA-1 remained normal.
Retinopathy	Usually develops, especially with long standing diabetes	The non- proliferative type occurred in one of the two patients who continued the honey therapy for more than 8 years
Peripheral neuropathy	Almost always occurs	It progressed in one of the 20 patient volunteers to a diabetic foot after 10-year honey intervention
Diabetic foot	Not uncommon even with good glycemic control	Developed in in one of the 20 patient volunteers after 10-year honey intervention, but it healed with topical honey
Renal failure as a result of diabetic nephropathy	May develop especially after a long duration of diabetes	Did not develop in any of the volunteers during the period of the honey therapy
Infections	Not uncommon, and serious infections may develop	Not frequent, but serious infections did not develop in any of the patient volunteers, except diabetic foot in one patient
Number of drugs	Many, including hypoglycemic agents, anti-hypertensive drugs, lipid controlling drugs, angina medications	Only one; honey
Side effects related to the drug	Common, and sometimes life threatening	Apart from its effects on diabetes, no side effects observed

Table 6: A proposed comparison between honey and the current medications in the treatment of type 2 diabetes and its associated metabolic disorders, based on the results of this pilot study. DKA: Diabetic Ketoacidosis; HHS: Hyperglycemic Hyperosmolar State; CHD: Coronary Heart disease.

As limitations of this study; investigations as testing for micro-albuminuria, and measurements of pH, serum osmolality, and serum bicarbonate, and anion gap were not done for all patients. Also, as a limitation of this study, the sample size was small; only 7 of the 20 patient volunteers continued the honey intervention for 2 years or more.

Conclusion

The author imposed on announcing these results, which might be of help for the patients with diabetes mellitus.

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