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Original Article

Effect of Four-week Honey-treatment on Blood Glucose and Lipid Profile in an Experimental Model of Diabetic Neuropathy

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ABSTRACT

Background and Aim: Honey is a natural substance with various medicinal properties which include antibacterial, antihypertensive, hepatoprotective, hypoglycemic and antioxidant effects. However, the role of honey in the management of neuropathic morbidities in diabetic neuropathy has not been studied. Especially, the effect of honey on fasting blood glucose and lipid profile in diabetic neuropathy has not been assessed. Therefore, in the present study we have assessed the effect of honey treatment on blood glucose and lipid profile in animal diabetic neuropathy model. **Methods:** Twenty-four healthy male Wistar albino rats of 10-12 weeks age, weighing 200±30 g were obtained from JIPMER central animal house. After one week of habituation, rats were divided into three groups randomly. After developing diabetic neuropathy, Fasting Blood Glucose (FBG) and lipid profile, Aspartate Transaminase (AST) and Alanine transaminase (ALT) were measured in blood sample in the rats before and after honey treatment. **Results:** Significant increase in FBG, AST, ALT and lipid profile except HDL cholesterol was seen in diabetic neuropathy when compared with normal healthy rats. There was a significant reduction in all these parameters except HDL-cholesterol after four-week honey treatment in comparison with diabetic neuropathy rats without treatment. **Conclusion:** Honey, given at a dose of 0.5 gm/kg BW for four weeks is effective in reducing blood glucose, atherogenic index and lipid profile and improving liver functions in albino rats.

Key words: Honey, Diabetic Neuropathy, Hyperglycemia, Hyperlipidemia.

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INTRODUCTION

Diabetes Mellitus (DM) is characterized by persistent hyperglycemia which results from defects in insulin secretion, insulin action, or both.[1] According to ICMR-INDIAB national study there are 62.4 million people with Type 2 Diabetes (T2DM) in India.[2] Diabetic Neuropathy (DN) is one of the most common long-term complications of diabetes affecting more than 50% of diabetic population. The presentation of DN is heterogeneous, affecting different parts of the nervous system that present with diverse clinical manifestations. Most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy and the autonomic neuropathies.[3] An abnormality of nerve conduction tests i.e., decreased Nerve Conduction Velocity (NCV), which is frequently subclinical, appears to be the first objective quantitative indicator of polyneuropathy.[4]

Uncontrolled hyperglycemia is the major reason for micro- and macrovascular complications in diabetic neuropathy. The major metabolic changes caused by hyperglycemia are increased polyolpathway flux, elevated oxygen free radical formation and advanced glycosylation. All of these factors appear to have a negative impact on nerve blood flow and NCV in diabetes.[5] Diabetes is not only a disease of changes in glucose metabolism, but also changes in lipid metabolism which contribute to cardiovascular complications. In spite of aggressive treatment, the diabetic patients continue to suffer from morbidity and mortality due to the cardiovascular complications.[6]

Honey is a natural substance with various medicinal properties which include antibacterial, antihypertensive, hepatoprotective, hypoglycemic and antioxidant effects. It comprises mainly of fructose and glucose along with other bioactive constituents such as assorted phenolic compounds, flavonoids, organic acids, enzymes and vitamins.[7,8] Studies have shown that honey exerts a hypoglycemic effect and ameliorates oxidative stress in streptozotocin-induced diabetic rats.[9] Honey is known to be anti-diabetic. However, to best of our knowledge, the role of honey in the management of neuropathic morbidities in chronic diabetes has not been studied yet. Especially, the effect of honey on fasting blood glucose and lipid profile in diabetic neuropathy has not been assessed. The experimentally-induced diabetic neuropathy provides an ideal model for studying the effect of honey on blood glucose and lipid profile. Therefore, in the present study we have assessed the effect of honey treatment on blood glucose and lipid profile in animal diabetic neuropathy model.

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MATERIALS AND METHODS

Animals

For this study, twenty-four healthy male Wistar albino rats of 10-12 weeks age, weighing 200±30 g were obtained from JIPMER central animal house. Approval of Scientific Advisory Committee and Institute Animal Ethics Committee, JIPMER, Puducherry were obtained. All the animals were housed in individual cages with 12/12 h light/dark cycle and food, water *ad libitum*, in 25 ± 2°C temperature. The animals were handled in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) Guidelines for the care and use of animals for experimental purposes.The animals were acclimatized to the animal room condition for at least one week prior to the experiment at the Animal Research Laboratory in the Department of Physiology, JIPMER following which the rats were divided into three groups randomly.

Group 1: Normal Control Group (NC) - rats received normal chow.

Group 2: Diabetic Neuropathy Control Group (DNC) - rats developed diabetic neuropathy and did not receive any treatment.

Group 3: Diabetic Neuropathy Honey Group (DNH) - rats developed diabetic neuropathy and received honey for 4 weeks.

Induction of Diabetic Neuropathy

NC group received normal chow diet throughout the study. DNC and DNH groups received high fat and high sugar diet for 8 weeks followed by streptozotocin injection at a dose of 35mg/kg BW, dissolved in citrate buffer. Streptozotocin injection was given intraperitoneally to induce type 2 diabetes in DNC and DNH group, where NC group rats were injected with citrate buffer of the same volume.[10] Three days after Streptozotocin injection, development of diabetes was confirmed by measuring glucose level in fasting blood samples. Glucose measurement was performed with an Accu-Chek Performa Glucometer, Roche Diabetes Care, Germany. Rats with blood glucose concentration of 200 mg/dl or higher were considered diabetic and were included in the study.[11] After the development of diabetes, rats were allowed to develop diabetic neuropathy and Nerve Conduction Study (NCS) was done at every second week to confirm diabetic neuropathy. All the sixteen rats developed diabetic neuropathy after 4 weeks. Measures of NCS were performed as per the guideline of Animal Models of Diabetic Complications Consortium (AMDCC) protocols;[12] and Oh SS *et al.* for the measures of NCV in mice.[13]

Biochemical Analysis

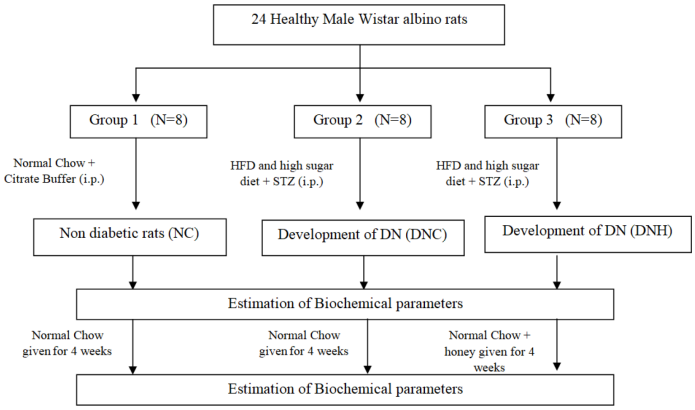
Blood sample was collected from retro-orbital sinus and the amount of Fasting Blood Glucose (FBG), Total Cholesterol (TC), Triglycerides (TG), LDL- Cholesterol (LDL-C), HDL Cholesterol (HDL-C), Aspartate Transaminase (AST) and Alanine Transaminase (ALT) in plasma were estimated using commercial reagent kits adapted to an ChemWell Awareness Technology Inc, fully automated clinical chemistry analyzer as per the manufacturer's instructions.

Treatment

After confirming the diabetic neuropathy, DNH group rats were given honey at a dose of 0.5 gm/kgBW, orally for a period of 4 weeks, whereas the NC and DNC group rats did not receive any treatment. Honey was procured from Green Planet Trust, Theni, Tamil Nadu, India, with approval of JSAC and Ethics committee.

Statistical Analysis of Data

SPSS version 19 was used for statistical analysis. The data were subjected to Kolmogorov-Smirnov normality test. All the data were expressed as mean ± SEM. The intergroup differences in mean were compared using Student's unpaired't'-test, for normally distributed data. Comparison of data between groups was done by using one-way ANOVA analysis. The association of Atherogenic Index (AI) with FBG and hepatic enzymes, was assessed by Pearson's correlation analysis. The difference was considered statistically significant if probability of chance was less than 0.05.



RESULTS

There was no change in the FBG and lipid profile in normal control group (Group 1) rats after the period of four weeks; similar results were observed in diabetic neuropathy control group (Group 2) rats.

Table 1 shows the comparison of parameters before and after four weeks of honey treatment in the diabetic neuropathy group (Group 3) rats. There was significant decrease in FBG, TC, TG, LDL-C, AI, AST and ALT, whereas the HDL-C was increased significantly. There was slight increase in body weight which was not significant.

Table 2 shows the comparison of all parameters between the groups before the initiation of treatment. The blood glucose and all lipid parameters except HDL-C and AST, ALT were significantly elevated in DNC and DNH group when compared to control group. Body weight

Table 1: Comparison of parameters in diabetic neuropathy rats after four weeks of honey treatment.

Parameter	Diabetic Neuropathy Honey Group - Pre (N=8)	Diabetic Neuropathy Honey Group - Post (N=8)	*P* value
Weight (gm)	223.00±7.81	229.00±5.48	0.5396
FBG (mg/dl)	479.45±8.34	364.23±10.26	<0.0001
TC (mg/dl)	159.06±6.43	77.33±5.81	<0.0001
TG (mg/dl)	198.99±13.07	63.50±3.75	<0.0001
HDL-C (mg/dl)	36.17±1.36	46.70±2.29	0.0014
LDL-C (mg/dl)	68.84±2.63	59.55±1.28	0.0067
AI	0.73±0.04	0.12±0.03	<0.0001
AST (IU/L)	258.50±12.12	202.73±11.11	0.0044
ALT (IU/L)	206.21±7.71	120.13±4.88	<0.0001

Values expressed as Mean ± SEM; Analysis done by Student's unpaired t test.

The *P* values less than 0.05 were considered statistically significant.

FBG: Fasting blood glucose, TC: Total Cholesterol, TG: Triglycerides, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, AI: Atherogenic Index, AST: Aspartate Transaminase, ALT: Alanine Transaminase.

Table 2: One Way ANOVA analysis of parameters between three groups before the initiation of treatment.

S.No	Parameters	Normal Control (N=8)	Diabetic Neuropathy Control (N=8)	Diabetic Neuropathy rats treated with Honey (N=8)
1	Body Wt (gm)	231.37±5.99	221.71±4.96	223±7.81
2	FBG (mg/dl)	96.12±2.05	479.33±6.29***	479.45±8.34***
3	TC (mg/dl)	111.98±2.65	160.36±9.01***	159.06±6.43***
4	TG (mg/dl)	53.48±1.68	200.02±10.43***	198.99±13.07***
5	HDL-C(mg/dl)	49.85±1.40	35.46±2.18***	36.17±1.36***
6	LDL-C (mg/dl)	57.10±1.09	69.55±3.13**	68.84±2.63**
7	AI	0.03±0.008	0.73±0.03***	0.73±0.04***
8	AST (IU/l)	136.25±7.52	260.30±12.73***	258.5±12.12***
9	ALT (IU/l)	89.87±3.81	207.2±6.98***	206.21±7.71***

Values expressed as Mean ± SEM; Analysis done by One-way ANOVA.

*Comparison with normal control group: *(*P*<0.05); **(*P*<0.01); ***(*P*<0.001)

FBG: Fasting Blood Glucose, TC: Total Cholesterol, TG: Triglycerides, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, AI: Atherogenic Index, AST: Aspartate Transaminase, ALT: Alanine Transaminase

Table 3: One Way ANOVA analysis of parameters between three groups after four weeks' time.

S.No	Parameters	Normal Control (N=8)	Diabetic Neuropathy Control (N=8)	Diabetic Neuropathy rats treated with Honey (N=8)
1	Body Wt (gm)	240.25±5.06	217.00±4.67*	229±5.48
2	FBG (mg/dl)	98.50±1.77	485.00 ±9.12***	364.23±10.26***,###
3	TC (mg/dl)	116.41 ± 3.53	172.25±5.43***	77.33±5.81***,###
4	TG (mg/dl)	55.97±1.90	208.85±11.86***	63.5±3.75###
5	HDL-C(mg/dl)	49.22±1.17	32.65±1.24***	46.7±2.29###
6	LDL-C (mg/dl)	59.6±2.25	74.17±1.80***	59.55±1.28###
7	AI	0.054±0.01	0.81±0.03***	0.125±0.03###
8	AST (IU/l)	138.12±3.56	269.13±10.31***	202.73±11.11***,###
9	ALT (IU/l)	93.00±3.61	214.53±4.63***	120.13±4.88***,###

Values expressed as Mean ± SEM; Analysis done by One-way ANOVA.

*Comparison with normal control group: *(*P*<0.05); **(*P*<0.01); ***(*P*<0.001),

#Comparison with diabetic control group:#(*P*<0.05); ##(*P*<0.01); ###(*P*<0.001).

FBG: Fasting Blood Glucose, TC: Total Cholesterol, TG: Triglycerides, HDL-C: High Density lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, AI: Atherogenic Index, AST: Aspartate Transaminase, ALT: Alanine Transaminase.

Table 4: Correlation of AI with various parameters of three groups.

Parameters	Normal Control		Diabetic Neuropathy Control		Diabetic Neuropathy with Honey	
	r	*P*	**r**	*P*	**r**	*P*
FBG	-0.6867	0.0600	0.7135	0.1113	0.7552	0.0825
AST	0.1863	0.6586	-0.3869	0.4486	0.3479	0.4992
ALT	-0.0891	0.8337	-0.069	0.8967	0.8164	0.0475

The *P* values less than 0.05 were considered statistically significant.

FBG: Fasting Blood Glucose; AST: Aspartate Transaminase, ALT: Alanine Trans-Aminase.

Table 5: Correlation of FBG with LFT parameters of three groups.

Parameters	Normal Control		Diabetic Neuropathy Control		Diabetic Neuropathy with Honey	
	r	*P*	r	*P*	r	*P*
AST	0.3938	0.3344	-0.3783	0.4596	0.6430	0.1684
ALT	-0.0808	0.8492	0.2265	0.6661	0.8486	0.0326

The *P* values less than 0.05 were considered statistically significant.

AST: Aspartate Transaminase, ALT: Alanine Transaminase.

and HDL-C were reduced in DNC and DNH group in comparison to NC group.

Table 3 shows the comparison of all parameters between the groups after 4 weeks' time. The diabetic neuropathy rats treated with honey showed significant decrease in blood glucose when compared with DNC group, but the values were still higher than the NC group. The TC, TG, LDL-C were decreased significantly in the diabetic neuropathy rats treated with honey in comparison with DNC group and there were no significant changes when compared with NC group. HDL-C was increased in DNH group in comparison with DNC group. AST and ALT parameters were significantly reduced in DNH group in comparison with DNC group and were significantly elevated when compared with NC group.

In the diabetic neuropathy group treated with honey, there was a positive correlation of AI with ALT as shown in Table 4; also, blood glucose was positively correlated with ALT (Table 5).

DISCUSSION

In the present study, the effects of four weeks ingestion of honey on FBG, lipid profile and hepatic enzymes were observed in experimental model of diabetic neuropathy. As such, ingestion of High-fat Diet (HFD) and high-sugar diet for eight weeks followed by single dose injection of STZ at a dose of 35 mg, i.p., was the procedure followed as the experimental model for developing type-2 diabetes in the present study, as this method has recently been practiced for effective induction of diabetes with the features of metabolic syndrome.[14] The present technique was adopted to develop a unique animal model that will mimic the pathological features seen in a large pool of individuals with long-term diabetes and metabolic syndrome, suitable for pharmaco-physiological screening of preparations such as honey, which has been reported to be beneficial in this condition.[15] Such a model should replicate the components of metabolic syndrome such as hyperlipidemia, hypertension and obesity along with type 2 diabetes mellitus. However, in the present study, we decided not to induce obesity in the experimental rats, as adiposity per se has been reported to profoundly influence insulin sensitivity, glucose and lipid metabolism, inflammatory markers and hepatic enzyme systems.[16] Therefore, in this study, we preferred to add high-sugar materials to the HFD to minimize the effect of weight gain while inducing diabetes in the rats. Thus, the body weight between control group and experimental group was not statistically significant (Table 2). Hence, we had body-weight matched diabetic and non-diabetic rats in this study, which is the novelty of the present work.

The streptozotocin and the alloxan models of chemically-induced diabetes are commonly used to screen anti-diabetic formulations. However, these methods cause marked destruction of the pancreatic cell mass and may therefore mimic changes closer to type 1 diabetes rather than type 2 diabetes mellitus. Recently, it has been reported that rats fed with HFD and combination of streptozotocin developed type 2 diabetes resemble more closely to humans.[17] HFD causes insulin resistance in peripheral tissues due to lipotoxicity, while, low dose of streptozotocin induces mild

defect in insulin secretion.[18] Combination of HFD with low dose streptozotocin model has therefore successfully mimicked natural progress of diabetes development as well as metabolic features in human type 2 diabetes. However, for the study of metabolic syndrome, several investigators have used carbohydrate (Fructose or sucrose) and fat-rich dietary components in rodents. Combinations of carbohydrate and fat-rich dietary components have been used in rodents to mimic these signs and symptoms of human metabolic syndrome.[14] Therefore, in the present study, we have used HFD and high-sugar diet for inducing diabetes in rats.

After the development of diabetes, rats were allowed few more weeks to remain diabetic till they developed neuropathy, which was confirmed by electrophysiological studies of the neurons. The main objective of the present study was to assess the effects of honey in diabetic neuropathy model, as neuropathy is the most common complication of Diabetes Mellitus (DM). Neuropathy occurs in more than 60% of the patients and affects their quality of life.[19] Worldwide, Diabetic Neuropathy (DN) is the leading cause of diabetes-related hospital admissions and non-traumatic amputations.[3] In order to identify the mechanisms and to devise new treatments of DN, it is necessary to select the precise animal model. The selected animal model of DN should exhibit the features present in human pathology and diabetic rats should show many abnormalities that are seen in diabetic patients with neuropathy, including hyperalgesia, allodynia, slow Nerve Conduction velocity (NCV) and progressive sensory and sensory motor deficit. Therefore, in this study we decided to select the rat model for assessment of effects of honey in these diabetic animals. Contributing factors to the neuropathy phenotype in rodents include background strain, diet composition, insulin/C-peptide deficiency, coexisting hyperglycemia and hypertension and duration of diabetes. Wistar rats are the ideal experimental species that fulfill most of these criteria of DN.[20] Therefore, in the present study we have used Wistar rats to investigate the effects and mechanism of action of honey with its potential activity in DN model as well to assess the etiological factors in the pathogenesis of DN.

Honey is reported to lower blood glucose in diabetic rats.[21-24] In our study, honey reduced blood glucose in diabetic neuropathy rat model, but not effectively as it did not reduce it to the level of that of normal control rats (Table 3). On the other hand, honey treatment reduced all the lipid parameters to the normal values except HDL cholesterol which was increased and this finding is similar to the study conducted by Ozra *et al*.[21] However, the glucose-reducing effect of honey has been attributed to its low-glycemic index.[25] A comparative study demonstrated that honey has lesser glycemic index against glucose or sucrose in healthy and type 1 diabetic individuals.[26] The same study conducted on type 2 diabetic patients exhibited similar values for honey, glucose and sucrose. Honey when contrasted with dextrose showed momentously low rise in plasma glucose levels in diabetics, with a reduction of serum triglycerides, homocysteine and C reactive protein levels in healthy and hyperlipidemic subjects.[27] The sugar is considered poisonous and toxic for diabetic patients and artificial sweeteners too do not help the cause. However, as diabetics have more craving for sweets, some alternative is needed for them. Since honey tastes sweet but has hypoglycemic effect, as it increases insulin secretion to reduce blood glucose levels.[28-29] Its usage seems practical over saccharine or sucrose for diabetic patients. In comparison to dextrose, honey shows reduced plasma glucose levels in healthy individuals. It also contains fructose, minerals flavonoids and antioxidants.[30] The fructose component of honey has been reported to enhance hepatic glucose uptake and glycogen storage while also reducing glycemia and insulin levels.[31] Therefore, hypoglycemic properties of honey makes it best suited for its use by diabetics.

In the present study, following honey treatment for four weeks, there was a profound decrease in TC, which was reduced than that of normal control rats. Total cholesterol is the major culprit in diabetic cardiovascular complications and invariably, diabetic neuropathy patients die not because of neuropathy but because of cardiovascular complications.[32] Thus, the hypolipidemic effect of honey could be protective factor in reducing the cardiovascular complications in diabetic neuropathy. Regular intake of honey reduce the plasma prostaglandins, cholesterol, triglycerides and homocysteine levels while also boosting antioxidants, serum iron, serum HDL levels and blood indices in both healthy and hyperlipidemic subjects.[28] In the present study, the Atherogenic Index (AI), which is an important marker of cardiovascular risk, was reduced considerably in experimental rats after four-week honey treatment (Table 1), indicating a substantial improvement in cardiometabolic status of these rats. Further, AI was significantly correlated with FBG and ALT (Table 4), which indicates that there could be a link of reduction in atherogenic lipid profile with improvement in hepatic glucose metabolism and hepatic enzyme activities.

Hepatic enzymes, AST and ALT were significantly reduced in diabetic neuropathy group after treatment with honey. Thus, honey could be a potential therapeutic agent in improving liver functions in diabetic neuropathy rats. Liver is the main organ of metabolism and honey has been reported to improve hepatic functions by inducing hepatic enzyme system.[33] The liver has been referred to as the primary controller of glycemia. Studies reported that fructose which is present in significant proportions in most honeys has been shown to enhance glucokinase and glycogen synthase activities and inhibit phosphorylase activity in the liver.[34-36] The net effects of these actions would tend to result in increased hepatic glucose phosphorylation, increased synthesis and decreased breakdown of glycogen in the liver. In the present study though we have not assessed the enzymes of hepatic glucose metabolism, the induction of AST and ALT indicate improvement of hepatic enzyme system and metabolic activity by four weeks treatment of honey in diabetic rats. Further, ALT was significantly correlated with FBG and the r value for AST was also quite high (Table 5) indicating that decrease in FBG could be due to increased clearance by the liver due to induction of hepatic functions resulting probably in gluco-metabolic enzymatic activities.

Independent of glycemic control, obesity and dyslipidemia are the risk factors for development of diabetic neuropathy.[37,38] Profound decrease in lipid levels following honey treatment, as found in our study, could be helpful in reducing these risk factors, also the glucotoxic effects on neural function may significantly reduce due to decrease in lipotoxic levels. However, this has to be assessed in future studies and also in human subjects. The present study is a preliminary report of four weeks oral treatment of honey in experimental diabetic neuropathy rats, in which there was significant reduction in FBG, lipid risk factors and enzymes of hepatic dysfunctions. Future studies should address, if improvement in these cardiometabolic profile in experimental diabetic rats could contribute to improvement in neuronal functions.

CONCLUSION

Honey given at a dose of 0.5 gm/kg BW for four weeks reduced fasting blood glucose and atherogenic index and lipid profile in type 2 diabetic neuropathy rat models. Also, honey improved liver functions in terms of reducing the increased-levels of AST and ALT in these experimental rats.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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