Scope of Honey in Diabetes and Metabolic Disorders

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Hilal Ahmad Wani, Sabhiya Majid, Mohsin Saleem Khan, Arif Akbar Bhat, Reyaz Ahmad Wani, Showkat Ahmad Bhat, Sadaf Ali, and Muneeb U. Rehman

Abstract

Metabolic disorders occur when unusual chemical reactions take place in the body amend usual metabolic pathways. Diabetes mellitus a metabolic disorder is generally characterized by high glucose level in blood over longer period of time. In type 1 diabetes, pancreas fails to produce adequate insulin and the same effect is due to the loss of beta cells of pancreas. Type 2 diabetes begins with resistance to insulin and accordingly gives no response to insulin. Gestational diabetes mellitus is similar to type 2 diabetes in various aspects and is having combination of inadequate insulin and sensitivity to it. For many years, honey is being used as a substitute for sugar and for providing medicinal benefits. In animal as well as human studies, convincing evidence specifies that honey displays antidiabetic as well as hypoglycemic effects. Additionally, honey consumption improved other disorders related to metabolism and to diabetes such as reduced levels of HbA1c (glycosylated hemoglobin) and hepatic transaminases and increased HDL cholesterol. The same was in addition to lowering hyperglycemia and oxidative

H. A. Wani
Department of Biochemistry, Govt. Degree College , Handwara, Jammu and Kashmir, India

S. Majid (✉)
Department of Biochemistry, Government Medical College, Srinagar, Jammu and Kashmir, India

Multidisciplinary Research Unit (MRU)-ICMR, Government Medical College, Srinagar, Jammu and Kashmir, India

M. S. Khan · A. A. Bhat · S. Ali · M. U. Rehman
Department of Biochemistry, Government Medical College, Srinagar, Jammu and Kashmir, India

R. A. Wani
Department of Paediatric Surgery, Government Medical College, Srinagar, Jammu and Kashmir, India

S. A. Bhat
Department of Biochemistry, Government. Medical College, Doda, Jammu and Kashmir, India

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stress. Besides depicting hypoglycemic effect, research has indicated that honey improves lipid anomalies in rats and humans suffering from diabetes. The beneficial effects of honey could also be limiting other disorders of metabolism and lessening damaging effects on various organs of the body that ultimately result in diabetic complications. Although there are few studies in the literature which are contrary to the above-depicted discussions regarding the beneficial effects of honey and its use in diabetic disorder. Also the clinical trials or studies on humans (both diabetic and healthy) are rather very sparse. It is anticipated that this book chapter will encourage fundamental investigation intended at explicating the mode of actions by which oligosaccharides present in honey improves antidiabetic/hypoglycemic effects.

Keywords

Metabolic disorders · Diabetes mellitus · Honey · Hypoglycemic

9.1 Introduction

9.1.1 Disorders of Metabolism

Metabolic disorders occur when unusual chemical reactions taking place in the body amend usual metabolic pathways. The metabolic processes take course in our body for getting and making energy from the food we eat and to sustain ourselves. Food that we normally consume is composed of carbohydrates, proteins and lipids. Besides there are also present some other constituents like nucleic acids, minerals, vitamins etc. Digestive juices secreted in our gastrointestinal tract break down the food consumed into simple sugars and acidic compounds which is our body's fuel. Upon complete digestion our body can use this food immediately or can store it in the cells and tissues like liver and muscles in the form of glycogen or fat depending upon the status of the body. Any disorder that occurs in these metabolic reactions may result in the disruption of these processes. When these disorders take place, we may have large quantities of some materials or small quantities of other ones that are needed for staying healthy without any disease. These metabolic disorders have been categorized into different groups. Some metabolic disorders may affect the metabolism of carbohydrates, amino acids, proteins, nucleic acids or lipids. Another group of metabolic disorders involving mitochondrial diseases affects those parts of cells that are involved in the production of the energy needed by the body. The metabolic disorders develop when some organs or cells, such as of liver or pancreas, are affected by some diseases and do not function in a normal way e.g., diabetes. The disorders may also be present hereditarily because of defined inherited gene anomalies which are mostly autosomal recessive (Graef et al. 2008). Metabolic disorders usually are associated with many symptoms like weight loss, lethargy, seizures and jaundice. These symptoms vary with the type of metabolic disorder. The symptoms have been grouped into four categories like acute, late-onset acute,

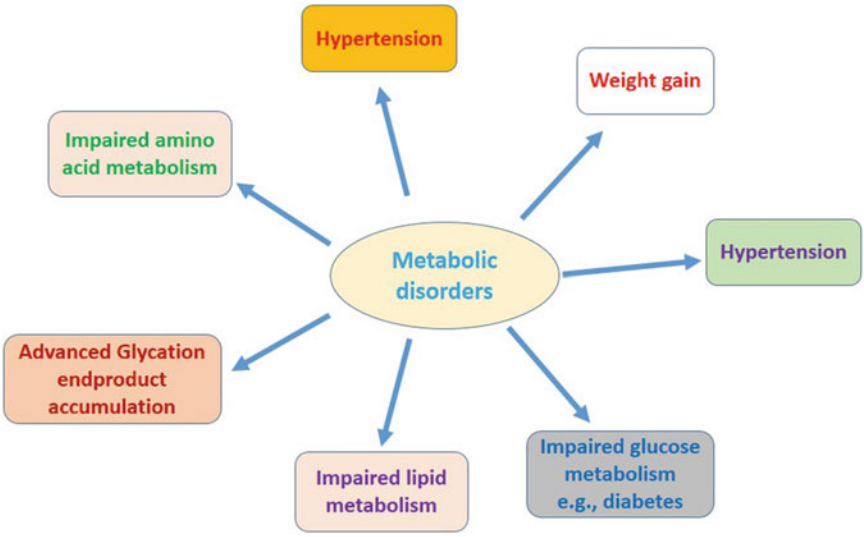

Fig. 9.1 Various disorders associated with metabolism

progressive general and permanent symptoms (Fernandes et al. 2013). In inherited metabolic disorders, because of defective genes, there occurs deficiency of some important enzymes involved in the metabolic processes. These disorders of multiple subtypes are commonly known as inborn errors of metabolism. Some metabolic disorders might also result because of the malfunction of liver or pancreas (Medline Plus 2018). The major groups of metabolic diseases are DNA repair-deficiency disorders, hyperlactatemia, iron metabolism disorders, acid-base imbalance, porphyrias, metabolic brain diseases, lipid metabolism disorders, glucose metabolism disorders, disorders of calcium metabolism, phosphorus metabolism disorders, water-electrolyte imbalance, metabolic syndrome X, malabsorption syndromes, wasting syndrome, mitochondrial diseases, inborn error of metabolism, metabolic skin diseases and proteostasis deficiencies. These disorders are diagnosed by specific screening tools and may be present from birth. If not diagnosed at an early stage, they get missed and get diagnosed at a later stage with the onset of symptoms. The tests available for their diagnoses include specific DNA and blood tests. The microflora residing in the gastrointestinal tract also plays an important role in metabolism with a symbiotic relationship with the host individual. These organisms generally consume undigested food and produce some important by-products for the host organism. Any pathophysiological abnormality in the gut microflora might play a role in metabolic-related obesity (Hur and Lee 2015). These disorders can be screened with the help of routine blood tests, genetic tests, skin tests etc. in newborns and if detected early these can be managed by the management of nutrition. Physicians or dietitians should have the knowledge of the disorder and the genotype of the individual so that they can accordingly plan the treatment that will be most

effective for the individual (Acosta 2010). Figure 9.1 depicts various disorders that are associated with metabolism.

9.1.2 Diabetes Disorder

As per a report in 2017, there were 425 million people who had developed diabetes throughout the world and the occurrence of diabetes has been found to be 8.8% among adults (IDF 2017). Overall, 90% of diabetic cases belong to Type 2 category. Rates have been found to be roughly equal in both genders as indicated by the data. However, males have been found to be more prone to the disease in many populations round the globe (Vos et al. 2012). As per a report of the World Health Organization (WHO), diabetes led to the death of 1.5 million people in 2012, thus making it one of the major causes of death in the world (WHO 2013a, b). As per a report of the International Diabetes Federation (IDF) published in 2017, diabetes caused 4.0 million deaths worldwide and the data were calculated using modelling to evaluate the number of deaths directly or indirectly linked to diabetes. It is also forecasted that globally the number of diabetics might escalate by 48% between 2017 and 2045 (IDF 2017).

Diabetes mellitus or simply diabetes is a metabolic disorder which is generally characterized by a high glucose level in the blood over a longer period of time (WHO 2014a, b). The symptoms of this metabolic disorder mostly include increased thirst, increased hunger and frequent urination. If the disorder is not treated, it can cause more complications which include hyperosmolar hyperglycaemic state, diabetic ketoacidosis or death. Besides, in diabetic patients many long-term complications might also happen over a prolonged period of time including chronic kidney disease, cognitive impairment, stroke, damage to the eyes, foot ulcers, cardiovascular disease and damage to the nerves (Saedi et al. 2016). The disorder mostly manifests itself because of the main reason of the pancreas not producing and secreting enough insulin or the cells of the individual are insensitive towards the insulin secreted by the pancreatic cells (Shoback and Gardner 2011). Diabetes disorder has been categorized into three main subtypes.

Type 1 diabetes: In this subtype of diabetes, the pancreas fails to produce and secrete adequate insulin and the same is due to the loss of beta cells of the pancreas. It was previously also known as insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes. The disease is mainly caused by the loss of beta cells of islets of Langerhans of the pancreas by autoimmunity. The cause of this abnormal autoimmunity is still unknown.

Type 2 diabetes: This disorder begins with resistance to insulin, a condition in which the cells become insensitive to insulin and accordingly give no response to insulin. If the disease continues the insulin deficiency may also develop. It was previously also known as non-insulin-dependent diabetes mellitus (IDDM) or adult-onset diabetes. The disorder mostly arises because of excessive body weight and lack of exercise.

Gestational diabetes: This is the third form of diabetes and is found exclusively in pregnant women who have high blood sugar levels without an earlier history of diabetes (WHO 2013a, b).

Diabetes can be prevented by modifying life style e.g., maintaining normal body weight, avoiding use of tobacco, regular physical exercise, a healthy diet and control of blood pressure. There should be proper eye care and foot care among the people with the disease. Type 1 diabetes is being managed by injecting insulin (WHO 2013a, b) while type 2 is treated by medication with or without the supplementation of insulin. Oral medications and insulin often lead to low blood sugar levels (Rippe and Irwin 2010). Gestational diabetes, which is commonly found in pregnant women usually, resolves of its own after the baby is delivered (Cash 2014).

The typical symptoms shown by a person with untreated diabetes include polyuria (frequent urination), polyphagia (more hunger), polydipsia (more thirst) and weight loss. In type 1 diabetes, the symptoms usually develop rapidly over weeks or months while in in type 2 diabetes the symptoms develop gradually or may be absent till the disease reaches the advanced stage. Diabetes patients also show symptoms of tiredness and weight loss (WHO 2019) besides others which can mark the onset of diabetes although these are not definitive to diabetes. Additionally, the diabetic patients may suffer from fatigue, headache, blurred vision, itchy skin and slow healing of cuts and wounds. Persistent high blood glucose level might lead to the absorption of glucose in the eye lens leading to the changes in it and hampering the normal vision of the person. The condition may also lead to diabetic retinopathy. Besides in diabetics there might occur a condition known as diabetic dermadromes which is characterized by skin rashes (Rockefeller 2015). Persons suffering from type 1 diabetes may also have episodes of diabetic ketoacidosis (DKA), which is a metabolic disorder characterized by vomiting, nausea, abdominal pain and in severe cases a reduced consciousness level and smell of acetone on the breath (Kitabchi et al. 2009).

The different forms of diabetes ultimately escalate the chances of long-term complications. Among these the primary complications which occur because of the damage of the small blood vessels include damage to the nerves, kidneys and eyes. Eye damage, commonly known as diabetic retinopathy, occurs because of the damage to the blood capillaries and vessels supplying to the eye, and this damage can culminate in vision loss and ultimate blindness (WHO 2014a, b). Besides, this disease increases the chances of developing cataracts, glaucoma and other eye-related problems. For the same reason patients with diabetes are recommended to visit an ophthalmologist at least once a year (Medline Plus 2018). Similarly, in diabetics any damage to the kidneys, which is known by diabetic nephropathy, results in urine protein loss, tissue scarring and eventually chronic kidney disease (CKD). These patients require frequent dialysis or permanent kidney transplantation. Also the diabetic patients might suffer from damage to neurons, and the condition is known as diabetic neuropathy which is the most common complication found in diabetic patients (WHO 2014a, b). This condition leads to tingling, pain, altered pain sensation, numbness and can further lead to skin damage.

Table 9.1 Comparative analysis of type 1 and type 2 diabetes (Source: Melmed et al. 2011)

	Diabetes	
Characteristic	Type 1	Type 2
Inception	Sudden	Gradual
Age at inception	Children mostly	Adults mostly
Size of body	Normal or thin	Obese often
Ketoacidosis	Common	Rare
Autoantibodies	Present (usually)	Absent
Insulin produced by body	Absent or low	Normal, increased or decreased
Concordance in identical twins	50%	90%
Incidence	~10%	~90%

Once diabetes was thought of a singular form but today it is a more variable disorder, and patients sometimes have more than one combination of forms (Tuomi et al. 2014). Broadly this disorder is categorized into four variable forms: type 1, type 2, gestational and other specific types (Shoback and Gardner 2011).

9.2 Type 1 Diabetes

In this type of diabetes, the insulin-producing beta cells of the pancreas are lost, which ultimately leads to the insulin deficiency. Type 1 diabetes is further classified as idiopathic or immune-mediated. Mostly this disorder is immune-mediated, where a T-cell-mediated autoimmunity attacks beta cells and destroys them, thus leading to insulin deficiency (Rother 2007). This type of diabetes constitutes about 10% of diabetes mellitus cases in Europe and North America. Mostly the people suffering from this order seem to be healthy and of normal weight when the onset occurs. These patients in the early stages of the disease show normal sensitivity and responsiveness. Due to the frequent occurrence in the children, the disorder was called as juvenile diabetes; however, the majority of the patients living with this disease are adults now (Chiang et al. 2014). The disease can occur at any stage of life. Type 1 diabetes shows inheritance partly linked with multiple genes including HLA genotypes as has been shown by the studies influencing the risk of diabetes.

9.3 Type 2 Diabetes

This type of disorder is characterized mostly by resistance to insulin but there may also be a reduced amount of insulin produced (Shoback and Gardner 2011). The insensitivity towards insulin seems to be because of the defective insulin receptor; however, the exact reasons are not known. The diabetic disorders with unknown reasons have been placed under a separate class. This disorder occurs commonly (WHO 2013a, b). In this type, people show evidence of prediabetic features (impaired blood glucose tolerance or impaired fasting blood glucose) before

developing type 2 diabetes (American Diabetes Association 2017). The progression of this disorder from prediabetes to type 2 diabetes can be reversed or reduced by some lifestyle medications that are known to improve sensitivity towards insulin or decrease the production of glucose by the liver (Carris et al. 2019). There are number of risk factors known that increase the chances of the disease of type 2 diabetes, e.g., stress, obesity (having body mass index (BMI) of more than 30), poor diet, lack of physical activity and urbanization (Melmed et al. 2011). The comparative analysis of type 1 and type 2 diabetes is summarized in Table 9.1.

9.4 Gestational Diabetes

Gestational diabetes mellitus (GDM) is similar to type 2 diabetes in various aspects and has a combination of inadequate insulin and sensitivity to it. It is commonly found in pregnant ladies with an incidence of about 2–10% and usually improves or disappears after delivery of the child. However, once the pregnancy is over, approximately 5–10% of women having GDM suffer from diabetes mellitus, most commonly type 2. This type of diabetes is fully curable; however, it requires careful medical intervention throughout the period of pregnancy. Its management includes dietary modifications, continuous blood glucose examination and in certain cases, insulin intervention is needed (NDIC 2011). If GDM remains untreated it has deleterious effects on the health of the foetus and mother. Risks to which the babies become prone in case of GDM include skeletal muscle defects, macrosomia (increased birth weight) and central nervous system anomalies and congenital heart.

9.5 Other Types

In this category there are a collection of diabetic disorders with few dozens of individual causes. MODY (maturity-onset diabetes of the young) is one of the disorders involving a rare inherited form of diabetes which is autosomal dominant and is because of several single-gene mutations leading to defects in insulin production (National Institute of Diabetes and Digestive and Kidney Diseases 2017). MODY is considerably less prevalent than the above-mentioned three types, accounting for 1–2% of all cases of diabetes. Occurring due to a faulty gene, MODY varies in severity and age at presentation as per the specific gene fault. Hence, 13 different subtypes of MODY are known. The individuals suffering from MODY are able to control the diabetes without insulin intervention (Thanabalasingham and Owen 2011). One form of diabetes arises because the body's receptors do not respond to insulin (although insulin levels are adequate, that is what separates it from type 2 diabetes); this form of diabetes is very rare. Mutations of genes (whether autosomal or mitochondrial) might also lead to faults in beta cells. In some cases abnormal insulin action may also be genetically determined. Damage to the pancreas by any disease has been found to lead to diabetes, e.g., cystic fibrosis and chronic pancreatitis. Besides diseases that are linked with too much

Table 9.2 Diagnostic criteria for diabetes set by WHO (World Health Organization 2006)

Situation	Glucose after 2 h	Glucose at fasting	HbA1c level	
Unit	mmol/L (mg/dL)	mmol/L (mg/dL)	mmol/mol	DCCT %
Normal	<7.8 (<140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥6.1(≥110) and <7.0(<126)	42–46	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	42–46	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥48	≥6.5

insulin secretion by antagonistic hormones may cause diabetes, and the same gets resolved once the excess hormone is removed.

The principal hormone that critically regulates the metabolism of glucose is insulin, and this hormone is involved in the regulation of glucose uptake from blood into the majority of cells of the body mostly liver, muscle (except smooth muscle) and adipose tissue. Consequently, the insensitivity of the cell receptors towards it plays a central role in various forms of diabetes (American Diabetes Association 2014). This hormone is used by almost two-thirds of the body's cells to absorb and utilize glucose as fuel from the blood; besides this hormone is also utilized for the conversion of glucose to other related forms required by the cells or for short-term storage. The stored form of glucose is then mobilized by the body during the times of fasting and is utilized for various purposes.

9.6 Characterization of Diabetes

Normally patients suffering from diabetes mellitus have persistent or frequent high levels of glucose in the blood. The disease is identified by following the below-mentioned criteria set by the WHO 1999. The diabetes diagnostic criteria adopted from the criteria set by WHO are also shown in Table 9.2.

- Plasma glucose level in fasting state ≥126 mg/dL (7.0 mmol/L)
- Blood glucose level ≥ 200 mg/dL (11.1 mmol/L) 2 h after the person is given 75 g oral glucose as is given in the oral glucose tolerance test (OGTT)
- Symptoms related to high blood sugar level and blood glucose ≥200 mg/dL (11.1 mmol/L)
- HbA1C (i.e., glycated haemoglobin) ≥ 48 mmol/mol (≥6.5 DCCT %) (Diabetes Care 2009).

For type 1 diabetes there is no recognized protective measure. However, type 2 diabetes that accounts for 85–90% of cases world over can often be delayed or prevented by engaging oneself in physical activity, sustaining normal body weight and consuming balanced diet (WHO 2013a, b). The effective lifestyle modifications

known to be helpful in preventing diabetes include consuming a diet rich in fibre and whole grains and consuming polyunsaturated fats found in nuts, fish and vegetables. Commonly used medications to treat diabetes mostly act by pulling down blood glucose levels through various mechanisms. Consensus is on the fact that when people suffering from diabetes maintain glucose control in the normal range, they do not experience or experience fewer problems like eye-related issues and kidney problems (MacIsaac et al. 2018). Insulin intervention is the only treatment available for type 1 diabetes and is given in the form of regular and NPH insulin or synthetic analogues of insulin. At a later stage, insulin can prove to be helpful in type 2 diabetes also. Some oral medications like metformin are available for type 2 diabetes, while other medications are available in the form of injectables, e.g., GLP-1 agonists. Metformin is being suggested as the drug of choice for type 2 diabetes as it has been shown to decrease mortality due to diabetes. The same drug works by reducing the production of glucose by liver. Besides metformin many other groups of drugs given orally may also reduce blood glucose level in type 2 diabetes. These drugs may upsurge insulin release, e.g., sulfonylureas, reduce absorption of sugar in the intestines, e.g., acarbose, increase the sensitivity of the body towards insulin, e.g., thiazolidinedione and increase elimination of glucose from the body through urine, e.g., SGLT2 inhibitors (Krentz and Bailey 2005).

Currently, the medical industry is shifting more and more on the health-related benefits of products of natural origin, herbs of medicinal importance and also honey for their usage in various ailments. With traditional medicines, including apicultural products like honey, together and in combination with standard medical treatments available, patients with different forms of diabetes can maintain normal insulin levels in the blood and also their overall health status.

9.7 Honey and Its Importance in Diabetes and Metabolic Disorders

Honey is produced by insects known as honeybees. The honeybees are associated with the genus *Apis*, and are known for making and storing of honey and for various ingredients that are actually useful to human beings. A widely appreciated honeybee product is the honey and is derived from the processing of nectar collected from different flowers and thereafter stockpiled in specialized honeycomb cells. Honey is generally promoted for its beneficial activities and has been promoted as a folk tonic since ages. Moreover, it is presented as a therapeutic agent in a clinical set-up (Molan 1999a, b). Honey has been proven very valuable because of its well-established role as an anti-cardiovascular, anti-microbial, anti-diabetic and anti-cancer agent (Alvarez-Suarez et al. 2016).

For many years, there was a myth that honey cannot be added in a diabetic patient's diet as it contains a high content of carbohydrates. As an amalgamated carbohydrate of biological origin, honey is frequently used as a natural sweetening agent and as a traditional therapeutic agent. There are different varieties of honey, and their grades differ in their glycaemic response and some varieties have a low

GI. The difference in glycaemic response has been suggested because of the different floral sources honeybees visit while collecting nectar and the fructose-to-glucose ratio (Bogdanov et al. 2008). With the help of modern or alternative medicine, in the past decade, thorough research had been accomplished so as to overcome the problems as observed in diabetes. For many years, honey is being used as a substitute for sugar and for providing medicinal benefits. In animal as well as in human studies, convincing evidence specifies that honey displays antidiabetic as well as hypoglycaemic effects (Al-Waili 2004a, b; Ahmad et al. 2008; Erejuwa et al. 2010, 2011a, b, c). However, proper mechanisms of anti-diabetic and hypoglycaemic effects are still in infancy and are rather unknown. Honey predominantly is composed of monosaccharides glucose and fructose which are easily absorbed in the small intestine of the GIT (Bogdanov et al. 2008). Honey is made up of more than 200 components with glucose, fructose and water as its main substances. Further, honey also contains many oligosaccharides and polysaccharides that are not digested easily and are not absorbed in the small intestine, but in the large intestine these components get digested by the intestinal microflora residing there (Bogdanov et al. 2008; Astwood et al. 1998; Sanz et al. 2005; Megherbi et al. 2009). Similarly, oligosaccharides and polysaccharides found mostly in plants such as chicory, garlic and onion are highly resistant to gastric juice and cannot be hydrolysed by the digestive enzymes present in the GIT of humans. However these are rich sources of nutrients for microflora present in the large intestine (Blaut 2002; Delzenne 2003; Gibson et al. 2004). Oligosaccharides are commonly viewed as prebiotics, and prebiotics are defined as those ingredients which are not digestible but beneficially affect the host by encouraging the growth or activity of one or limited number of bacteria residing in the colon selectively, thus improving the health of the host. As per the recently updated definition, a prebiotic consumed through diet is a selectively fermented ingredient of the food consumed that marks specific changes in the activity and composition of the microbiota living in the gastrointestinal tract, thus giving benefits to the host's health (Gibson and Roberfroid 1995; Gibson et al. 2010). Among these prebiotics, galacto-oligosaccharides, lactulose and fructo-oligosaccharides are commonly investigated (Gibson et al. 2004). Isomalto-oligosaccharides and xylo-oligosaccharides are similarly other oligosaccharides that have been assessed for their prebiotic effects (Gibson and Roberfroid 1995; van Loo et al. 1999a, b). Certain food substances including meals high in fruits, vegetables and low in fat and other oligosaccharides have been stated to reduce the occurrence of chronic ailments such as diabetes mellitus, hypertension, metabolic syndrome and insulin resistance (Alvarez-Sala Walther et al. 1996; Dall'Agnol and von Poser 2000; Feeney 2004; Heber 2004; Englyst and Englyst 2005; Cani et al. 2007). This chapter brings the latest results that reveal the valuable effects of oligosaccharides in improving diabetes mellitus, insulin resistance and obesity. Because of the similarities of these convincing findings with those of honey, several studies have been undertaken to authenticate the hypothesised findings that oligosaccharides existing in honey might contribute to the beneficial effects related to health and anti-diabetic effects. It is also expected that this will ignite a renewed interest in exploration of these beneficial effects of honey

and will help to encompass the frontiers of this exciting field and supplement the existing literature. Hence, this chapter accredited diverse scientific studies that have been conducted on honey in this regard, validating the beneficial effects of honey in its use in a complex disease like diabetes mellitus in clinical/preclinical studies, and animal and human trials.

9.8 Effect of Fructose and the Hypoglycaemic Effect of Honey

The content of fructose in honey varies from 21 to 43% and the fructose/glucose ratio from 0.4 to 1.6 or even higher. Fructose being the sweetest naturally occurring monosaccharide has a glycaemic index of 19 in comparison to glucose having a glycaemic index of 100 or sucrose which is refined sugar with glycaemic index of 60 (Bahrami et al. 2009; Deibert et al. 2010; Bantle 2009). Many studies have been conducted that have revealed the hypoglycaemic and anti-diabetic effect of the various constituents of honey, but the mechanisms of action of these remain still unclear. It has been suggested that selective mineral ions (copper, vanadium, selenium and zinc), phenolic acids, flavonoids and fructose might have a significant role in the process of benefits to the individuals (Erejuwa et al. 2010; Bahrami et al. 2009; Al-Waili 2003a, b). There is strong indication that fructose tends to reduce blood sugar levels in animal models with diabetes (Kwon et al. 2008; Erejuwa et al. 2012a, b). The mechanisms that seem to be involved in hypoglycaemic and anti-diabetic effects may include reduced degree of intestinal absorption of sugars, prolonged emptying time in stomach and less food consumption (Kellet et al. 2008; Moran and McHugh 1981; Gregory et al. 1989; Thibault 1994; Meirelles et al. 2011). Glucokinase present in hepatocytes has been shown to be activated by fructose and that has a significant part in the glucose uptake and storage in the form of glycogen by the hepatocytes. Glucose present in honey has been found to enhance the absorption of fructose in the intestine and has been noticed to promote its hepatic actions by its improved delivery to the liver cells (Fujisawa et al. 1991; Ushijima et al. 1995). The pancreas is an important organ as far as diabetes is concerned because it secretes two major hormones, insulin and glucagon, that regulate the level of glucose in the blood, and honey has been proposed to protect this important organ against damage and oxidative stress as it is rich in antioxidants. Thus this is an indirect potential mechanism by which honey exerts its antidiabetic effect (Erejuwa et al. 2010). In rat models, fructose administrated in the form of sucrose or alone improved homeostasis of glucose and response to insulin compared to the rats receiving glucose (Prieto et al. 2004). Other related studies demonstrated that in normal or type 2 model diabetic rats, fructose supplementation led to lower levels of blood insulin and blood glucose compared to the rats in which other sugars were administered (Kwon et al. 2008).

Various models of animals have been used for experimental studies depicting the possible glucose-lowering effect of honey, and the frequently used experimental method for prompting type 1 and type 2 diabetes in these models is alloxan and streptozotocin in proper dosages (Srinivasan et al. 2005; Lenzen 2008; Akhtar and

Khan 1989; Fasanmade and Alabi 2008). A study conducted over a period of 6 weeks on non-diabetic healthy rats fed with a diet containing honey depicted promising results. The weight was decreased significantly, but no substantial decrease in glycosylated haemoglobin (HbA1c) or intake of food was perceived (Chepulis 2007). Honey feeding for a longer period of time (i.e., 52 weeks) in Sprague-Dawley rats brought a noteworthy reduction of glycated haemoglobin levels but the same augmented HDL cholesterol levels (Chepulis and Starkey 2008). In rats fed with diet containing sucrose but not sugar, the HDL cholesterol levels were reduced without showing other differences as far as other lipids were concerned. Similarly the rats fed with sugar-free diet containing honey depicted weight gain compared to only sucrose-fed rats. In a study healthy rats were fed with 65/100 g combined fructose and glucose or a diet with honey for 2 weeks and in these rats it was observed that the fructose level in blood, vitamin E in serum and vitamin E/triglycerides in serum increased while blood glucose level remained unaffected and content of triglycerides reduced (Busseroles et al. 2002). In another study conducted by Nemoseck et al., healthy rats were given a diet containing 20% honey for 33 consecutive days. The study depicted significant reduction of leptin content, triglycerides, food/energy intake, epididymal fat weight and body weight but there was not any significant decrease in the glucose level, C-reactive proteins, total cholesterol and adiponectin. This trial depicted that feeding must be used for longer periods so as to get substantial results (Nemoseck et al. 2011a, b). There were no substantial differences in body weight or fasting blood sugar level in rats fed with honey and as honey was proved to have a glucose-lowering effect in healthy animals, the similar helpful effect was witnessed in prompted diabetic models (Erejuwa et al. 2010). There is an important observation with regard to honey and diabetes that in induced diabetic models, honey augments the effect mediated by anti-hyperglycaemic and anti-diabetic drugs (Erejuwa et al. 2010, 2011a, b, c). Alloxan-induced diabetic rabbits were used in one of the experiments, and to these rabbits, three kinds of sweeteners were given along with the diet. Unadulterated honey of *Apis dorsata* and *Apis florea* and adulterated honey were fed to these rabbits and a dose-dependent rise in the blood sugar level was registered in these rabbits (Akhtar and Khan 1989). In other studies, diabetes was induced in rats with the help of alloxan. The diabetic rats were fed with honey and the healthy rats were fed with fructose, and it was observed that the glucose level in blood decreased significantly in diabetic rats and insignificantly in fructose-fed rats (Fasanmade and Alabi 2008). Similar results were again seen in diabetic rats fed with honey which reduced hyperglycaemia (Erejuwa et al. 2009, 2010, 2011a, b, c). Similar to the previous findings of oligosaccharides on insulin level, diabetic rats when given a treatment with honey augmented blood insulin level, and the mass of beta-cell improved (Erejuwa et al. 2011a, b, c). When the healthy and induced type 2 rats were supplemented with honey, there was less body weight gain and reduced food intake (Nemoseck et al. 2011a, b; Bahrami et al. 2009). Alike to the possible effect of oligosaccharides as hepatoprotective agents, honey supplementation also showed hepatoprotective function in STZ-induced diabetic rats (Erejuwa et al. 2011a, b, c). Honey administration was also found to ameliorate aflatoxin-induced

histopathological changes in mice (Ezz El-Arab et al. 2006) besides intravenous honey injection also prompted a defensive effect against carbon tetrachloride (CCl4) induced hepatic damage (Al-Waili 2003a, b, c).

9.9 Effect of Honey and Other Sugars on Diabetes: Human Clinical Trials

Carbohydrates, proteins, lipids, water, minerals, vitamins, bioactive compounds and amino acids are required by humans for all biological activities and these compounds are obtained from the diet. The diet of humans must have all types of ingredients required for the metabolic alterations and for life support. Consumption of each of these ingredients and nutrients is the key factor for maintaining a healthy life in general. As a starting point different kinds of diseases have distortions in the metabolic pathways because of the absence or superfluous amount of one or more nutrients. Diabetes mellitus, as already discussed, manifests in the form of high blood glucose level in blood due to insufficient or no insulin production in the body. Studies on experimental animals proposed the helpful properties of honey as a diet supplement, and the studies also depicted control of diabetes mellitus and additional complications in animal models. However, the studies or trials on human beings both healthy and diabetic are rather sparse. Still there are some published studies that depict the beneficial properties of honey in both diabetic and healthy subjects (Yaghoobi et al. 2008a, b; Bahrami et al. 2009; Ahmad et al. 2008; Abdulrahman et al. 2011; Al-Waili 2003a, b, 2004a, b; Agarwal et al. 2007b). The antioxidant properties of honey are very significant as oxidative stress is associated and chiefly responsible for diabetes disorder (Gheldorf et al. 2003). In a study conducted on healthy, diabetics or patients with hyper-triglycerides in blood depicted promising results when their diet was supplemented with honey compared to the diet with only sucrose and dextrose (Al-Waili 2004a, b). Consequently, the profile of lipids was improved, elevated and normal C reactive protein was reduced. Besides, triacylglycerol and homocysteine value were also reduced in hyper-triglyceridemic patients. In diabetic patients, honey produced significantly lower rise of blood glucose level (BGL) compared with dextrose. Honey boosted insulin in comparison to sucrose, and after consumption at different times, it decreased blood homocysteine, CRP and lipids in normal subjects. The final conclusion was that honey led to lower elevation of PGL in diabetic patients compared to sucrose and dextrose.

Sugar being a polished and refined product is obtained from various natural sources and is processed through technological processes which result in the form of a pure substance called sucrose, which is highly used in various food industries and in modern life. Comparatively honey being also a natural product with sweet taste has a multifarious composition compared to sucrose and is supposed to have a lower energetic value and glycaemic index. The exact chemical composition of refined sugars can be easily stated compared to honey where many aspects have to be considered while stating its composition. Geographical and botanical origins are very helpful in determining the specific properties and composition of various types

of honey. Although the exact mode of action by which honey exerts its helpful effects on the level of blood glucose is not so clear, however from various comparative studies some assumptions depicting the significance of fructose present in honey have been drawn. Fructose in honey has been found to stimulate an important enzyme, glucokinase, in liver cells, which plays a significant part in the glucose uptake and its storage as glycogen by the hepatocytes of liver, thus supporting for its hypoglycaemic effect (Van Schaftingen and Vandercammen 1989).

In a study conducted at Erciyes University, Kayseri, Turkey, 20 healthy volunteers were taken. 50 g of pure glucose dissolved in 250 mL water was given to each of them besides honey in an amount corresponding to 50 g of glucose (calculated according to the physicochemical analysis of honey) was also given to the them. After consumption, on the next morning blood samples (capillary blood samples) were collected from the finger of the volunteers and again after every 15 min and after second consumption of sugars on the next day, until 120 min. Serum insulin and glucose level reduced after 2 h of intake of honey, and C peptide level slightly augmented 2 h after intake of honey. This trial validated that how various honey types of honey with diverse GI values influenced in a different manner on various parameters usually calculated and taken for analysing diabetes control (Soylu et al. 2015). In another related study conducted at Isfahan University of Medical Science, Iran, 60 healthy and normal subjects whose age ranged between 18 and 30 years were enrolled. The subjects received 80 g sucrose dissolved in 250 mL water and 80 g of honey once a day for consecutive 6 weeks. FBS (fasting blood sugar), SBP (systolic blood pressure) and DBP (diastolic blood pressure) were analysed from each participating subject at the start and at the end of the trial. Insignificant change was recorded in SBP and DBP in both groups at the start and at the end of the trial, but FBS enumerated a substantial reduction in the group fed with honey in comparison to the group receiving sucrose at the end of the study (Rasad et al. 2014). As already mentioned earlier, different studies depict that honey intake decreases the weight of the body and blood glucose level in diabetic patients and healthy subjects in comparison to sugar intake. A study conducted on type 2 diabetic patients who consumed natural honey showed that body weight was reduced and so were blood glucose and blood lipids. The study included patients suffering from type 2 diabetes, having fasting blood glucose of 110–220 mg/dL, and were on the same oral hypoglycaemic drug but not on insulin treatment. The investigational group ($n = 25$) received natural honey for 8 consecutive weeks while as the control group ($n = 23$) did not receive natural honey or any other sweetener. The fasting blood sugar levels and weight of the body was measured after every 2 weeks, and continuous decline was registered (Bahrami et al. 2009). Scientific studies also demonstrated that oligosaccharides and fructose in the honey contributed to the hypoglycaemic effect shown by honey. Additionally honey consumption improved other disorders related to metabolism and diabetes such as reduced levels of HbA1c (glycosylated haemoglobin) and hepatic transaminases and increased HDL cholesterol. The same was in addition to lowering hyperglycaemia and oxidative stress (Erejuwa et al. 2012a, b; Bahrami et al. 2009). Further, as stated for oligosaccharides (Yamashita et al. 1984; Cani et al. 2006a, b), honey supplementation showed similar

results and reduced glycaemic response in the postprandial state in type 1 diabetic patients and healthy volunteers (Samanta et al. 1985). Similarly, decline in blood glucose level was testified in subjects with impairment in glucose tolerance (Agrawal et al. 2007a, b). Likewise, as predicted for oligosaccharides (Luo et al. 1996, 2000; Alles et al. 1999; Causey et al. 2000), some studies did not show any substantial effect of honey on the blood glucose levels or on the insulin levels in patients suffering from diabetes (Bornet et al. 1985; Katsilambros et al. 1988; Nemoseck et al. 2011a, b). Bahrami and his co-workers depicted that honey-supplemented diet in patients suffering from type 2 diabetes did not produce any substantial effect on fasting blood sugar levels. However, it increased levels of HbA1c (glycosylated haemoglobin) (Bahrami et al. 2009). Supporting to data depicting the effect of oligosaccharides on lipid metabolism (Fiordaliso et al. 1995; Daubioul et al. 2000), honey supplemented diet substantially decreased LDL cholesterol, TG and TC, while it augmented HDL cholesterol in patients suffering from type 2 diabetes or in healthy persons (Bahrami et al. 2009; Yaghoobi et al. 2008a, b). In obese or overweight individuals, honey-supplemented diet slightly reduced or did not increase the weight of the body (Yaghoobi et al. 2008a, b). Similar results depicting loss of weight or decreased intake of food was reported as a consequence of oligofructose-supplemented diet in obese, overweight or healthy individuals (Delmee et al. 2006; Cani et al. 2006a, b; Parnell and Reimer 2009).

9.10 Honey and Its Role in Diabetic Wound Healing

In addition to the beneficial health effects of consuming or ingesting natural honey in diabetes and other metabolic disorders, honey could also find important beneficial effects in managing wounds of diabetic patients (Alam et al. 2014). These wounds found in diabetic patients are not like classic wounds; they heal very slowly or sometimes these wounds do not heal at all, leading to problems where conventional medicines do not have any effect. Honey has been used as a medicine for the healing of wounds since time immemorial while its use in diabetic wound management is recent. Patients suffering from diabetes sometimes suffer from many other complications like vascular problems, arterial disease, foot complications and ulcerations (Singh et al. 2005; Lavery et al. 2007). Although diabetic wounds are to some extent similar to wounds of normal patients, the healing ability in diabetic wounds is problematic and slow besides the medical expenditures are very high. Honey has been found to be a possible choice to be used in diabetic wounds because of it being natural, its large availability and its inexpensive nature. Honey, when diluted with water and applied at the wound site, forms hypochlorite anions and hydroxyl radicals. Also at the site of the wound the antioxidants found in honey mostly act by two dissimilar mechanisms: first, these fight against microbes and reduce the infection in the wound and second, these antioxidants decrease ROS (reactive oxygen species) generation and inflammation of the wound, thus helping in the healing process (Cooper et al. 1999; Estevinho et al. 2008; Mathews and

Binnington 2002). Also the antibacterial activity of honey is attributed to its osmotic effect, acidic pH, nitric oxide and hydrogen peroxide. The presence of nitric oxide and the production of NO by honey in various body fluids increase the rate of healing (Al-Waili and Saleeb 2003). Scar formation, inflammation control, debridement and wound odour are very important as far as diabetic wound management is concerned (Alam et al. 2014). The slow healing of diabetic wounds is attributed to peripheral neuropathy and peripheral arterial diseases that are associated with diabetes where the blood vessels tend to shrink and, ultimately, decrease the circulation of blood to the respective areas. The nerves become damaged and more vulnerable to injury as these do not receive enough nutrients via blood. The tissue growth stimulus is induced when honey is used because of the chemical composition, the presence of vitamins, assimilable sugars, phenolics and amino acids, which increased the supply of nutrients and oxygen in the diabetic wound area (Molan 1999a, b; Molan 2002). Application of honey decreased the intensity of ulcer pain and reduced the ulcer size along with deodorization at the wound site. Besides it reduced the healing time of wounds and without any side effects. A recent study has brought forth a new indication demonstrating the beneficial properties of Manuka honey in wound management, and the outcomes reported by the researchers in this study depicted that honey improved the responsiveness against oxidative damage and it also stimulated proliferation of cells. This could better help to understand how Manuka honey developed its effect on the healing of wounds (Alvarez-Suarez et al. 2016). Although there are some guidelines for proper honey applications in wound management, it is stated that natural unheated honey should be usually used in treatments and it should be stored in amber-colored glass bottles and in cool places. Different standardised medical grade honey have been formulated with antibacterial activity which find their use in wound management and treatment, e.g., Woundcare 18+ (Comvita: Te Puke, New Zealand), Medihoney (Capilano: Richmonds, Queensland, Australia) and Apiban (Apimed: Cambridge, New Zealand) (Molan 2002). If not available, any dark coloured honey with extraordinary antimicrobial activity may be used.

Based on the findings we hypothesize that saccharides, mostly oligo, present in honey might be contributing to the anti-glycaemic/anti-diabetic effects and may also be involved in reducing other metabolic disorders. Considering the availability of few studies and dearth of large-scale data, especially large controlled randomized clinical trials, we strongly have confidence in that future research on honey should not only be limited to exploring the therapeutic and beneficial potential alone but should also include trials and studies designed at revealing the composite mechanisms of action mediated by honey. It is anticipated that this chapter will encourage fundamental investigation intended at explicating the mode of actions by which oligosaccharides present in honey improves anti-diabetic/hypoglycaemic effects. This will definitely help to further encompass the boundaries of facts with regard to the benefits of honey.

9.11 Summary

Metabolic disorders occur when unusual chemical reactions taking place in the body amend usual metabolic pathways. Diabetes mellitus or simply diabetes is a metabolic disorder which is generally characterized by a high glucose level in blood over a longer period of time. In type 1 diabetes, the pancreas fails to produce and secrete adequate insulin and this is due to the loss of beta cells of the pancreas. Type 2 diabetes begins with resistance to insulin, a condition in which the cells become insensitive to insulin and accordingly give no response to insulin. Gestational diabetes mellitus is similar to type 2 diabetes in various aspects and is having a combination of inadequate insulin and sensitivity to it. It is commonly found in pregnant ladies. For many years, honey is being used as a substitute for sugar and for providing medicinal benefits. In animal as well as in human studies, convincing evidence specifies that honey displays anti-diabetic as well as hypoglycaemic effects. Additionally honey consumption improved other disorders related to metabolism and diabetes such as reduced levels of HbA1c (glycosylated haemoglobin) and hepatic transaminases and increased HDL cholesterol. The same was in addition to lowering hyperglycaemia and oxidative stress. Besides depicting a hypoglycaemic effect, research has indicated that honey improves lipid anomalies in rats and and diabetes in humans. The beneficial effects of honey could also be limiting other disorders of metabolism and lessening the damaging effects on various organs of the body that ultimately result in diabetic complications. There are few studies in the literature which are contrary to the above-depicted discussions regarding the beneficial effects of honey and its use in diabetic disorder. Also the clinical trials or studies on humans both diabetic and healthy are rather very sparse. It is anticipated that this chapter will encourage fundamental investigation intended at explicating the mode of actions by which oligosaccharides present in honey improves anti-diabetic/hypoglycaemic effects.

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