

Nutritional Components Relevant to Type-2-Diabetes: Dietary Sources, Metabolic Functions and Glycaemic Effects

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ABSTRACT

Type-2-diabetes mellitus (T2DM) is a global non-communicable disease with dietary causes. This chronic disease is escalating to epidemic proportion. Medication expenditure puts additional burden on the nations already deprived of economy due to loss in terms of disability adjusted life years. Since there is no permanent cure as yet, dietary prevention and management remains the best mitigation strategy. Hyperglycemia is the characteristic symptom of T2DM. The glycaemic propensity of the food/diet is regulated at bio-accessibility, bio-availability and metabolic levels and is determined by the nutrient content and composition. Though qualitative information of certain dietary components on glycaemic regulation of the foods has been documented, studies pertaining to their effect and mechanisms have been fragmentary across several reports over the period of many years. Therefore, the present review has been conducted to interpret individual and synergistic effects of the most relevant nutritional components on the glucose propensity, insulin secretion and insulin sensitivity. This review identifies and enlists some of the most relevant nutrients to T2DM; provides various dietary sources along with their content in the context of their glycaemic indices and tracks the physiological participation of amino acid, fatty acids, cholesterol and dietary fiber. The pertinence of the nutritional components to different aspects of diabetic pathophysiology has been categorized. This study is of significance in formulations of diet and food supplements, meal planning as well as nutrition policy and regulation. Some of the identified nutrients may also function as metabolic biomarkers for prognosis and as potential therapeutic agents.

Key words: Glycaemic index, Nutrient, Composition, Insulin resistance, Glycosylated haemoglobin, Type 2 diabetes mellitus, Insulin secretion, Insulin sensitivity, Dietary fiber, Polyphenol, Bioactive compound, Pathophysiology of diabetes, Nutrient metabolism, Nutraceutical, Oxidative stress

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INTRODUCTION

Diabetes generally represents paraphernalia of metabolic disorders which are primarily characterized by high levels of blood sugar over a prolonged period of time. The prevalence of type 2 diabetes mellitus (T2DM) and the associated complications are on the rise. Diabetes is a life style disease with dietary causes. Insulin is the key glucoregulatory hormone produced by the pancreatic β -cells that regulates blood glucose

levels [1]. Diabetes occurs when the pancreas is unable to produce sufficient amounts of insulin or the cells of the body cannot effectively utilize the insulin produced by them [2]. Dysregulation in the glucose homeostatic mechanism may lead to acute or chronic hyperglycemia [3]. This chronic condition is further characterized by alterations in protein and lipid metabolism [4] resulting from defects in insulin production and/or reduced insulin sensitivity [1]. There are primarily three types of diabetes:

1. Type 1 diabetes mellitus (T1DM) is characterized by an autoimmune destruction of the pancreatic

beta-cells and frequently observed in the pediatric population group [4]. It is also known as insulin dependent diabetes mellitus or "juvenile diabetes" due to its prevalence among children and adolescents [5].

- 2. T2DM is characterized by a state of insulin resistance wherein the pancreatic β -cells cannot function effectively in terms of insulin secretion. This type is frequently observed in the adult population and is the most common type of diabetes constituting 95% of total diabetes cases [4]. This form of diabetes is also referred to as non-insulin dependent diabetes or "adult-onset" diabetes since it is commonly diagnosed later in life.
- Type 3 diabetes mellitus (T3DM) refers to 'brain diabetes' characterized by reduction in the expression of insulin and neuronal insulin receptors leading to development of insulin resistance in the brain of patients with Alzheimer's disease [6,7]. Pathophysiological changes in neuronal stress and PI3K-GSK3β signaling as well as inflammation overlap with Alzheimer's disease and T2DM [8]. Vanadium was suggested as beneficial element for T3DM as vanadate was found to inhibit tyrosine phosphatase [9].

Additional secondary forms of diabetes include gestational diabetes mellitus (GDM), characterized by hyperglycemia during pregnancy in women without a previous history of diabetes. Certain other forms of diabetes manifest from prolonged use of glucocorticoids or occur as a ramification of diseases such as Cushing's syndrome, cystic fibrosis, neonatal diabetes and defects in genes regulating insulin secretion [4].

Prevalence of diabetes

By the year 2017, it was estimated that 451 million people above the age of 18 years were affected with diabetes with total health care expenditure of USD 850 billion and about 5 million deaths in the age range of 20 to 99 years were attributed to diabetes on worldwide basis [10]. About 50% of diabetic cases remained undiagnosed. An estimated 374 million people had impaired glucose tolerance and about 21.3 million women had some or other forms of hyperglycaemia.

Normal carbohydrate and insulin metabolism in normal condition

Dietary carbohydrates such as starch and glycogen are acted upon by mouth salivary alpha amylase breaking them down to oligosaccharides and disaccharides (Table 1). In small intestine, the pancreatic alpha amylase, sucrase, maltase and lactase breaks them into monosaccharaides (glucose, fructose, and galactose) which are absorbed through small intestinal lining into the bloodstream. Glucose transporter protein-1 (GLUT-1) helps them across the epithelial cells [10]. Insulin is an anabolic polypeptide hormone which is secreted by β -cells in the islets of Langerhans of the endocrine pancreas adjacent to duodenum. The full chemical structure of the insulin was fully worked out in the year 1953 by Sanger [11]. Glucose that is released into the blood after digestion is an important trigger for secretion of insulin. Glucose enters the beta cell by glucose transporter protein-2 (GLUT2) receptor. Adenosine tri phosphate (ATP) thus generated inactivates potassium channel protein leading to membrane depolarization and release/secretion of insulin. Amino acids, fatty acids and ketone bodies also play a similar role in insulin secretion. Incretins released from the gut after consumption of food also stimulate insulin secretion. Insulin binding to the receptor stimulates translocation of glucose transporter protein-4 (GLUT4) to the cell surface [12]. Glucose is then transported into the cell and undergoes metabolism. In muscle cells, entry of glucose leads to glycogen and protein synthesis and inhibit protein degradation. Insulin is directly associated with amino acid uptake and conversion into protein. In liver, insulin stimulates glycogen synthesis and lipogenesis and inhibits gluconeogenesis. Insulin converts excess carbohydrates into glycogen in liver and muscles. In adipose tissue, insulin promotes lipogenesis and inhibits lipolysis. Insulin affects mainly carbohydrate, protein and fat metabolism [13]. In adipose tissue, the carbohydrates are converted into fats by the mediation of

Table 1.	Dolo of mutuitional	common on to in	alwaa ami'a waawlatia	m and raduation a	f diabatia miale
Table I:	Role of nutritional	components in s	pivcaemic regulatio	л апо геоисион о	i diadelic risk

Nutritional Component	Food	Nutrient Content	Effect	Reference
	Emmer			[14,15]
	Spelt wheat			
Alkylresorcinol	Whole wheat grain	0.4 to 55.8 mg/100 g	Inhibits activity of alpha-glucosidase enzyme	
	Rye			
	Barley			
Alpha-linolenic acid	Flaxseed, walnuts, and vegetable oils, canola and soybean oils	0.2 to 11.0 g/100 g Fat	Reduces pancreatic damage; Ameliorates insulin level; Exhibits anti-oxidative	[16]
	Bran layer of grains			l [17]
	Whole grain		Viscosity hinders digestive enzyme access and glucose	
Arabinoxylan	Aleurone layer	2.37 to 30 g/100 g	absorption; Improve insulin resistance and post prandial	
	Rye		glucose response	
	Wheat			

	Aleurone layer			
	Bran layer			
Beta glucan	Whole grains			
	Barley	0.4 to 3.9 g/100 g	Improves insulin sensitivity	[17]
	Oat			
	Rye	_		
	Wheat			
Detaine	Whole wheat	0.1.() 00.4 /10.0		F4 41
Betaine	Spelt wheat	0.16 to 294 mg/100 g	Overcomes insulin resistance	[14]
	Grains			
Mara in a sital	Nuts	225 to 1500	Cytoprotective effects; Positive effect on pancreatic	[10]
Myo-inositol	Fruits	= 225 to 1500 mg/day	secretion of insulin by insulin-dependent signaling	[18]
	Vegetables		cascade meenamism, improves insum resistance	
	Common wheat			
	Spelt wheat			
	Baked beans			
Carbohydrates	Chick peas	4.5 to 74.48 g/100 g	Lowers triglycerides, HbA1c and C-reactive protein	[19]
	kidney beans		(CRP)	
Rve	Rye			
	Soy beverages			
Chlorogenic acid	Coffee	1 g/day	Inhibits digestive enzymes; Blocks sodium dependent glucose transporter SGLT1 in small intestine; stimulates insulin secretion and activates insulin receptors	[20]
	Cereals		F	
	Legumes	_	Binds with low molecular weight oligopeptides and	
Chromium	Vegetables	— 50 to 200 μg/day	influences insulin metabolism; Lowers blood glucose	[21]
	Fruits		and HDATC and Improves insum sensitivity	
	Brown rice			
	Soybean		Regulates glycosylated haemoglobin; Participates in colonic formentation and generation of short chain fatty.	
Dietary fibre	Flaxseeds		acids: reduces starch susceptibility to digestive enzymes:	[22]
5	Legumes		SCFA modulate gluconeogenesis and lipogenesis; lowers	
	Whole grains		HbA1c	
	Whole grains			
Fats	Legumes	0.38 to 35 g/100 g	Increases LDL Cholesterol, triglycerides and HbA1c	[19]
	Soy bean			[]
	Cereals		Madulatas glusosa from blood to muscle, promotos	
Ferulic Acid	Legumes	 25 to 3300 mg/100 g	insulin secretion: blocks sodium dependent glucose	[20]
i ei une i ieu	Nuts		transporter SGLT1 in small intestine	[=0]
	Whole grains			
Phenolic Acids	Legumes	- 0.11 to 117.1 mg/100 g	Inhibition of α -amylase and α -glucosidase activities	[14,23, 24]
	Bran laver			
Phytic Acid	Whole grains	 0.9 to 15.2 σ/100 σ	a-alucosidase and a-amplase inhibition	[17]
i nyuc Aciu	Legumes	0.7 to 13.2 g/ 100 g	u-grucosidase and u-aniyidse minoritori	[1/]
	Brown algan		Anti avidativo mashaniam, in bibita -lucasa val	
Polyphenol	Whole wheat	0.15 g/100 g	Anu-oxidative mechanism; inhibits glucose release from carbohydrate source: improves insulin resistance	[25,26]
	Coroala			
Protein	Logumos	- 2.08 to 17.47 g/100 g	vegetable protein poses lesser risk of 12D than animal	[27]
	Drupolla vulgaria			
Triterpenic Acid	Contolla anistic	- 0.34 to 8.5 mg/100 g	Increase insulin sensitivity; anti-obesity; decrease	[28]
·· · ·	Centella asiafica	asiatica g	giucose production, and oxidant, enzymatic regulation	

insulin. Myo-inositol, a carbocyclic sugar found in grains and nuts also benefits in T2DM, aid in insulin dependent signal cascade and increases insulin sensitivity (Table 1). Almost upto 400 mg/100 g of myo-inositol was noted in blue berry with corresponding GI of 59.

Insulin metabolism in diabetic condition

In chronic diabetic condition, due to hindered insulin secretion, effects contrary to normal health materialize

such as increase in lipolysis leading to generation of fatty acids; increase in small dense low density lipoproteins (LDL), increased level of hepatic triglycerides; decrease in high density lipoproteins (HDL); higher rate of gluconeogenesis and decrease in protein synthesis [29,30]. Insulin deficiency leads to lipolysis of the fat and release of free fatty acids due to activation of lipase. These fatty acids are then used as source of energy. Excess intake of fat during insulin deficiency leads to ketosis and acidosis [31].

Pathophysiology of diabetes

The increasing interest in research in diabetes has led to a better understanding of the pathophysiology of the disease and thereby development of several antihyperglycaemic interventions. The combined effects of genetic constitution, lifestyle changes and aging increase the overall risk of diabetes. These factors contribute to hyperglycaemia through mechanisms of impaired insulin secretion and impaired insulin action in target cells (insulin resistance) which jointly contribute towards the development of pathophysiological conditions [31]. The schematic representation of T2DM pathophysiology is presented in Figure 1. The post prandial glucose molecules enter into the pancreatic β -cell by means of GLUT2. The intracellular glucose enters into glycolysis and Krebs cycle in mitochondria, generating ATP molecules. With the increase in ATP: ADP ratio, the potassium channel gets blocked. Consequently, with altered potential due to higher level of positively charged potassium ions, the membrane gets depolarized. This activates voltage dependent calcium channel causing



Figure 1: Diagrammatic representation of pathophysiology in type 2 diabetes mellitus (T2DM) (a) Glucose transporter type 2 (GLUT2) membrane transporters facilitates entry of post prandial blood glucose into the cell. Intracellular glucose is phosphorylated by glucose-6-phosphatase to glucose-6-phosphate that enters glycolysis cycle generating pyruvate and adenosine triphosphate (ATP). Pyruvate enters tricarboxylic acid (TCA)cycle further generating ATP. Increase in ATP: ADP ratio blocks KATP channel leading to membrane depolarization thus letting Ca²⁺ ions into the cell through voltage dependent/gated calcium channel. Ca²⁺ ions stimulate the secretion of insulin peptide; (b) In healthy individuals, insulin binds to insulin receptor which initiates phosphorylation based signaling cascade that results in translocation of intracellular GLUT4 to membrane for uptake of glucose molecules; (c) In diabetic condition, insulin receptors become non-functional and cytoplasmic GLUT4 does not get translocated to membrane resulting in insulin resistance. Consequently, glucose uptake does not take place which leads to hyperglycemia (increased blood sugar levels).

influx of calcium ions. The calcium ions cause expression of transcriptional activators such as hepatocyte nuclear factor 1 alpha (HNF1A) and 4 alpha (HNF4A) which initiates insulin synthesis and secretion.

Impaired β -cell function (generally observed prior to clinical onset of the disease) leads to impaired insulin secretion which is clinically observed as a decline in the glucose responsiveness of the cells in the pancreas [32]. Impaired glucose tolerance (IGT), characterized by decrease in glucose-responsive insulin secretion post meals causes hyperglycaemia. Associated risk factors such as glucose toxicity and lipotoxicity further enhance the progression of impaired insulin secretion. If this condition remain untreated, it would result in overworking of the pancreatic β -cells, leading to progression of apoptosis and finally a decline in the pancreatic β -cell mass (the product of β -cell size and number) [33]. The progressive decline of pancreatic β -cell function and mass over time accompanied with elevation in the blood glucose level (hyperglycaemia) marks the development of T2DM [34,35].

Insulin resistance occurs when the cells of the body fail to respond to physiological levels of insulin that is produced, causing an increase in the level of blood glucose [36]. In peripheral cells, under healthy condition, the insulin peptide binds to the insulin receptor triggering phosphorylation based signal cascade which translocates GLUT4 from cytoplasm to membrane (Figure 1). GLUT4 then facilitates uptake of glucose into cells and inhibits the usage of reserve fats for energy [32]. However, under diabetic condition, insulin receptors in the cells of peripheral tissues become inactive and GLUT4 remains in the cytoplasm. Therefore, the cells cannot absorb glucose contributing to the development of chronic hyperglycemia [37]. T2DM is essentially a result of combination of inhibition of insulin secretion and insulin resistance as influenced by genetic determinants, [38] level of physical activity, dietary pattern, aging and lifestyle [39,40]. Excessive intake of carbohydrates, oils and fat leads to hyperglycemia and hyperlipidemia causing nutrient overload and imbalance. Prolonged exposure to such over nutrition leads to lipid peroxidation and glycation. These developments result in insulin resistance. These factors, along with consumption of energy-rich foods are crucial contributors to the development of T2DM [40,41].

Diagnostic parameters of diabetes

Prominent symptoms of diabetes include polyuria, polydipsia, weight loss, and blurred vision. Certain long term complications result in retinopathy, peripheral neuropathy, nephropathy, foot ulcers and kidney failure [42]. Diabetes is a major risk factor for periodontitis, a chronic disease affecting periodontal ligament and alveolar bone [43]. A direct and proportional relation between severity of periodontitis and diabetic complications was observed from cross sectional, prospective and interventional studies [44]. The glycated haemoglobin (HbA1c) is a marker for chronic glycaemia which measures the percentage of blood sugar attached to hemoglobin. Conventional therapy for periodontal treatment even led to 0.4% reduction in HbA1c [45]. According to the American Diabetes Association (ADA), the diagnosis of diabetes is usually based on the glucose criteria, wherein fasting plasma glucose (FPG) or the 75 g oral glucose tolerance test (OGTT) are the most widely accepted diagnostic tests. A FBS value \geq 126 mg/dl is considered diabetic [46]. The HbA1c test is a widely used diagnostic test which indicates the average blood sugar levels over the past 60 to 90 days. The ADA affirmed that an individual with a HbA1c percentage of \geq 6.5 is diabetic and a percentage of 5.7-6.4 indicates pre-diabetes [42]. The risk and incidence of diabetes is measured in terms of glycaemic index (GI), HbA1c or insulin resistance. Diet composition plays prominent role in the management of disease symptoms. There are several nutritional components in the diet that has relevance to the risk of diabetes either directly or indirectly.

There are several reports that indicate the GI and glycaemic load (GL) of foods. However, reports pertaining to the role and effect of nutritional components on glycaemic potential were fragmentary and scarce. Structuring and engineering of food components within the food matrix with a control on its digestion and their bioavailability has been proposed for meeting the nutritional requirements of vulnerable population groups [47]. Therefore, the current review was undertaken to qualitatively and quantitatively estimate the effect of the nutritional components on the modulation of glycaemic propensity. The metabolic events associated with modulation of GI for each component has also been indicated that have clinical relevance.

Role of nutritional components in blood glucose regulation

Nutrition plays a key role in prevention of diseases and is essential to maintain a healthy lifestyle and accurate functioning of the body metabolism. Intake rates of nutrients were linked to body weight as well. Altered fat, carbohydrate and cereal fiber intake with low GI food consumption correlates to lower body weight. Different nutritional components that are found to be associated with glycaemic metabolism along with the range of their concentrations in diverse food sources and their effects on insulin secretion, insulin sensitivity and blood glucose level are summarized in Table 1. T2DM patients tend to consume foods containing nutrients in a pattern that is quite different to the normal subjects. Based on a cross sectional study, Breen et al. have observed that T2DM patients consume relatively higher amounts of total fat, monounsaturated fat and polyunsaturated fat and protein but the intake of carbohydrates, non-milk sugars and dietary fiber were relatively lesser than nondiabetic subjects [48].

In T2DM, dietary causes are considered more reliable and prominent risk factors when compared to genetic, epigenetic or environmental factors [49]. Although clinical factors such as conditions of overweight and obesity are risk factors, it can be observed that diabetes manifests even in individuals with normal body mass index (BMI). It is quite evident that the energy metabolism linked to nutrient metabolism is very relevant to T2DM. The energy imbalance that predisposes an individual for diabetes is either regulated by physical activity or diet composition of the food. In case of lack of physical utilization of excess glucose, diet regulation comes to the prominence in management of diabetes. An imbalance between the actual demand of energy within the cells and the extent of nutrient availability is the fundamental and pivotal in the development of T2DM [50]. Consumption of a diabetic diet, including complex carbohydrates, vegetables, lentils and generally, foods with a low GI and GL cause a modest rise in blood sugar which is essential in preventing long-term complications in T2DM. Therefore, there is possibility of reduction in its prevalence by dietary management. For effective dietary policy, it is important to have updated information on the role of different dietary components on blood glucose levels. Different nutritional components that have relevance to the metabolic glycaemic effects have been enlisted in Table 2 along with their dietary food

Table 2: Quantitative information of T2DM related nutrients, their food sources and corresponding glycaemic indices

Nutrient	Food	Content	GI	Reference
Insoluble	Whole sorghum flour	25.37 g/100 g	77.2	[78]
dietary fiber	Watermelon	0.3 to 0.6	76 ± 4	[79,80]
	Sapota	9.1 to 10.9	-	[79]
Soluble dietary	Whole sorghum flour	0.97 g/100 g	77 ± 8	[78-81]
fiber	Coconut flour	0.3 g/100 g	<55	[82,83]
	Wheat flour	2.4 g/100 g	74 ± 2	[80,82]
	Blue berry	100 to 400 mg/100 g	59	[84]
Myo-inositol	Cow milk	4 mg/100 g	31 ± 2	[84]
	Pea	5 to 20 µmol/g	22	[85]
	Wheat	2.37 to 10.75 g/100 g	74 ± 2	[80,86]
	Barley	4 to 8 g/100 g	28 ± 2	[87]
	Rye	8.60%	29	[88]
	Wheat flour	1.35 to 2.75 %	74 ± 2	[89]
Arabinoxylan	Whole rye	8.60%	29	[88]
	Wheat flour	5.53 to 7.19%	74 ± 2	[80,90]
	Rice	2 to 3%	73 ± 4	[83,90]
	Barley	3.98 to 5.44%	28 ± 2	[90,80]
	Maize	1 to 2%	59	[83,90]
	Rye	6.9 to 7.6%	29	[83,90]
	Wheat	0.48 g/100 g	74 ± 2	[91]
	Barley	4.16 g/100 g	28 ± 2	[91]
Beta glucan	Oat	4.40%	50	[92]
	Whole sorghum flour	0.12 g	77 ± 8	[78,81]

	Mucuna seeds	5.28 g/16 gN	-	[93]
	Brown rice	7.69 g/100 g protein	68 ± 4	[80,94]
L-Arginine	Milk	3.09 to 3.25 g/100 g protein	15-60	[94]
	Legumes	5.58 to 8.83 g/100 g protein	12-70	[94]
	Mucuna seeds	7.88 g/16 gN	-	[93]
	Brown rice	8.40 g/100 g protein	68 ± 4	[94]
Leucine	Milk	9.83 to 10.66 g/100 g protein	15-60	[94]
	Legumes	6.73 to 8.91 g/100 g protein	12-70	[94]
	Mucuna seeds	4.16 g/16gN	-	[93]
	Brown rice	4.08 g/100 g protein	68 ± 4	[94]
Isoleucine	Milk	5.30 to 6.20 g/100 g protein	15-60	[94]
	Legumes	3.38 to 4.34 g/100 g protein	12-70	[94]
	Mucuna seeds	4.23 g/16 gN		[93]
	Brown rice	6.72 g/100 g protein	68 ± 4	[94]
Valine	Milk	5.86 to 6.40 g/100 g protein	15-60	[94]
	Legumes	4.09 to 5.53 g/100 g protein	12-70	[94]
	Wheat	0.2 g/100 g bran	74 ± 2	[94]
	Barley	0.3 g/100 g bran	28 ± 2	[94]
Alpha-linolenic	Pumpkin seed oil	<1%	-	[95]
Aciu	Cooked dry legume	2.5 to 41.7% of fatty acids	12-70	[96]
	Canola oil	44% of fatty acids		[97]
	Brown rice	16.10 mg/100 g	68 ± 4	[94]
Triterpenic acid	Cooked dry legume	0.34 to 8.5 mg/100 g	12-70	[96]
Oleanolic acid	Apples	0.28 g/100 g	36 ± 2	[94]
Oleanolic acid	Olive	0.18 to 3.10 g/100 g	-	[98]
Lupeol	Aloe vera	0.10 g/100 g	-	[98]
Acetate	Coconut flour	140 mmol	-	[82]
	Wheat flour	355 mmol	74 ± 2	[94]
Propionate	Coconut flour	47 mmol	-	[82]
-	Wheat flour	86 mmol	74 ± 2	[94]
Butyrate	Loconut flour	173 mmol	74 . 2	[82]
	wneat flour	225 mmol	/4±2	[94]
	Brown rice	1.38 mcg/100 g	08 ± 4	[94]
Biotin	Barley	2.38 mcg/100 g	20 ± 2	[94]
	Banana	mcvg/100 g	51 ± 3	[94]
	Darley Pumpkin cood	27.1 to 75.1	20 ± 2	[94]
Vitamin E	oil	27.1 to 75.1 mcg/g	-	[95]
	legume	mg/100 g	12-70	[96]
	Brown rice	0.69 mg/100 g	68 ± 4	[94]

	Milk	1.22 to 1.63 mcg/100 g	39 ± 3	[94]
Vitamin D	Orange	0.34 mcg/100 g	43 ± 3	[94]
	Chickpea	1.75 to 1.93 mcg/100 g	28 ± 9	[94]
	Wheat	3.27 mg/100 g	74 ± 2	[94]
Iron	Barley	2.5 mg/100 g	28 ± 2	[94]
11011	Brown rice	1.02 mg/100 g	68 ± 4	[94]
	Pineapple pulp	2.53 mg/100 g	65	[94,99]
	Wheat	109 mg/100 g	74 ± 2	[94]
Magnesium	Barley	79 mg/100 g	28 ± 2	[94]
	Brown rice	93.91 mg/100 g	68 ± 4	[94]
	Wheat	36 mg/100 g	74 ± 2	[94]
Calcium	Barley	29 mg/100 g	28 ± 2	[94]
Guicium	Brown rice	10.93 mg/100 g	68 ± 4	[94]
	Pineapple pulp	10.41 mg/100 g	65	[94,99]
	Brown rice	0.005 mg/100 g	68 ± 4	[94]
Chromium	Soybean	0.003 to 0.007 mg/100 g	16 ± 1	[94]
	Pineapple	0.008 mg/100 g	59 ± 8	[94]
	Cooked dry legume	11.8 to 25.9 mg GAE/100 g	12-70	[96]
Polyphenol	Whole sorghum flour	833	77.2	[79]
	Coconut flour	49	-	[82]
	Brown rice	2.81 mg/100 g	68 ± 4	[94]
	Brown rice	0.06 mg/100 g	68 ± 4	[94]
Chlorogenic	Apple	1.44 to 2.15 mg/100 g	36 ± 2	[94]
aciu	Water melon	0.51 to 0.58 mg/100 g	76 ± 4	[94]
	Brown rice	0.02 mg/100 g	66 ± 5	[94]
Ferulic acid	Apple	0.31 to 0.79 mg/100 g	36 ± 2	[94]
	Orange	0.19 mg/100 g	43 ± 3	[94]
	Wheat	0.03-0.15 g/100 g	74 ± 2	[94]
	Barley	42-51 mcg/g	28 ± 2	[94]
	Wheat	489 to 1429 mcg/g	74 ± 2	[94]
Alkylresorcinol	Rye	720 to 761 mcg/g	29	[100]
5	wheat	439 to 647 mcg/g	74 ± 2	[100]
	Barley	42 to 51 mcg/g	28 ± 2	[100]
	Wheat	412 mcg/g	74 ± 2	[101]
	Rye	110 mg/100 g	29	[100]
	Wheat	80 mg/100 g	74 ± 2	[100]
	Brown rice	742 mg/100 g	66 ± 5	[94]
Phytic acid	Barley	386 mg/100 g	28 ± 2	[94]
	Kidney bean	465-481 mg/100 g	24 ± 4	[94]
	White rice	1.3 HU/mg	72 ± 9	[102]
	Potato	5.5 HU/mg	70 ± 8	[102]
Lectin	Banana	13 HU/mg	62 ± 9	[102]
	Soybeans 87 HU/mg		15 ± 5	[102]
	Chick pea	180 HU/mg	36 ± 5	[102]

sources and corresponding GI values. However, it has to be noted that the GI value of food is determined by the complete nutritional composition and energy content of the food or diet. Unlike GL, which is solely concerned with the carbohydrate content in the food/diet, GI provides comprehensive representation of the entire food/diet composition [51]. Fat, starch and alcohol intake was positively associated with average GI. Intakes of mono and disaccharides and fibers were inversely associated with GI. Radovanovic et al. have observed that when Ierusalem artichoke was used as functional food source in developing extruded food, it has lowered the GI [52]. Such property was attributed to contribution in terms of high total dietary fiber content, and lower protein, carbohydrate and lipids. Murakami et al. observed that dietary GI was positively correlated with starch and GL and negatively associated with saturated fatty acids (SFA), total sugars, dietary fiber and total fat (in men) among British adults and there was no correlation of GI with total carbohydrates [53]. There was also no association between GI and BMI in both men and women. Burger et al. have reported that intake of high dietary fiber was inversely associated with mortality risk whereas higher intake of carbohydrates and sugars was positively associated with mortality risk among diabetic individuals with normal weight [54]. Goletzke et al. have observed that among pregnant women, dietary GI was inversely associated with micronutrient intake [55]. Higher GI was negatively correlated to intake of calcium, dietary fiber, riboflavin, folate, potassium, and magnesium intakes. Turner-McGrievy et al. have observed that consumption of vegan diet or conventional diabetes diet for 22 weeks in 99 participants increased carbohydrate, fiber and several micronutrients and improved alternate health eating index (AHEI) which was negatively correlated to HbA1c [56]. Intake of monounsaturated fatty acids (MUFA), polyphenols and fiber leads to improved endothelial vascular activity, lipid profile, anti-oxidative and anti-inflammatory mechanisms. These improvements cause glucose control in terms of HbA1c. Individual fatty acids such as linoleic and alpha-linolenic acid were found to have protective effect on pancreas by virtue of their antioxidant activity (Table 1) [16].

Recently, functional and novel food sources such as spelt wheat have been identified as appropriate dietary source compared to common wheat [57]. This is due to occurrence of substantial amounts of blood glucose lowering and multiple bioactive components such as dietary fiber, phytic acid, alkylresorcinols and antioxidants (Table 1). These components are known to regulate blood glucose level and optimize insulin sensitivity. Though the macronutrients play an important role in glycaemic response, the micronutrients and the bioactive components act either individually or in a synergistic manner. The higher protein content and fat content particularly that of unsaturated fat in spelt wheat favored glycaemic control.

When an imbalance occurs in the food intake and energy expenditure, the condition leads to excess nutrient

availability in the human body. Fats are stored as body fat mass leading to adiposity. The changes send nutrient related signals to brain. Nutritional changes also lead to impaired insulin secreting beta-cell functioning, diabetic nephropathy or even cardiac disease or atherosclerosis. Impaired glucose and lipid metabolism leads to fatty liver, neurodegeneration and inflammation. Elevated concentrations of the nutrients such as glucose, lipids and amino acids lead to vascular complications and injury to the insulin sensitive tissues. Insulin deficiency leads to decrease in the cellular uptake of glucose, increased protein catabolism, and increased lipolysis. Hyperglycaemia causes glucosuria, osmotic diuresis and electrolyte depletion. Increase in the amino acid content in blood plasma leads to loss of nitrogen through urine. Increase in free fatty acids in plasma leads to ketogenesis, ketouria and ketonemia. All these abnormalities due to altered nutrient metabolism lead to dehydration and acidosis which is a major concern. Nutrition therapy is effective in reducing the impact of higher blood glucose level. Dworatzek et al. reported that nutrition therapy has the potential to improve clinical outcomes by reducing HbA1c by 1% to 2% and have emphasized that replacing high GI carbohydrate foods with low GI foods can be helpful in management of T2DM [23]. In addition to the macronutrient composition of the food particularly that of protein and carbohydrates, the food physical state also has substantial effect on the post prandial blood glucose level. Shafaeizadeh et al. have reported that liquid foods differing in carbohydrate quality, produced glucose response that were comparable whereas solid formulations with similar protein and energy density elicited different GI and insulin responses [58].

However, it was previously noted that nutrient overloading does not cause any change in the mitochondrial oxidative capacity [59]. The changes in the nutrient availability during fasting and feeding are sensed by β -cells of the pancreas which engage in the release of insulin accordingly [60]. Insulin sensitivity in different tissues is related with redox balance and mitochondrial function. The nutrients modulate different metabolic pathways that exert control on insulin functioning [61]. Herbal formulations have been detailed by Adapa et al. [62] for treatment of diabetes. Precision nutrition has been suggested for prevention and management of diabetes [63].

Role of protein and amino acids

Consumption of legumes and more specifically that of lentils was found to be inversely associated with incidence of T2DM in adults [64]. It is well known that legumes are rich source of proteins. It was found that protein intake does not alter the glycaemic indicators. In T2DM individuals, intake of protein leads to better insulin response. Several studies have shown that replacing animal protein with plant protein has beneficial effects on the glycaemic control [27,65]. In an independent study, Malik et al. have reported that total protein and animal protein intake raised the risk of T2DM by 7% and 13%, respectively [27]. However, intake of vegetable protein caused moderate decrease in such risk [27]. A possible mechanism could be the presence of higher amounts of L-arginine in plant proteins than animal proteins [65]. In vitro studies and randomized controlled trials suggest that L-arginine promotes insulin secretion from β -cells and improves insulin sensitivity in T2DM [66-68]. L-Arginine is a cationically charged polar amino acid which causes membrane depolarization. This allows calcium ion influx into the β -cells which mediates insulin exocytosis (Figure 2). The distribution of L-arginine was found to be dense in brown rice, macuna seeds, milk and legumes (Table 2). Contrastingly, based on randomized parallel group study, Sucher et al. have reported that animal and plant protein have similar improvement in metabolism and cardiovascular risk factors in T2DM people and difference in amino acid composition does not affect metabolic responses [69]. This reveals that the glycemic modulation depends more on the amino acid composition rather than the source of protein.

Dietary amino acids such as alanine, L-arginine and glutamine as well as branched chain amino acid such as leucine participate in ATP producing tricarboxylic acid cycle (TCA cycle) at different stages.

Pyruvate is generated from alanine (by transamination) and glucose (by glycolysis). Acetyl CoA is generated from pyruvate (by oxidation) and leucine (transamination and dehydrogenation). Glutamine gets converted to α -ketoglutarate. The reducing equivalents from TCA cycle generates electrons that participate in electron chain transport chain resulting in phosphorylation of ADP to ATP by ATP synthase. When ATP: ADP ratio increase, ATP sensitive potassium channel (KATP) open, causing membrane depolarization. Consequently, voltage gated calcium channel (VGCC) gets activated allowing Ca²⁺ into the cell promoting calcium dependent exocytosis of insulin [70].

Dipeptidyl aminopeptidase IV (DPP-IV) such as gliptins, degrade incretin peptide hormones that regulates blood glucose level. Such activity is demonstrated in biological models [71]. Food hydrolysates may contain DPP-IV inhibitory peptide motif thus effecting antidiabetic activity [72]. Branched chain amino acids (BCAA) as well as aromatic amino acids such as isoleucine, leucine, valine, tyrosine, and phenyl alanine can be used as nutrient biomarkers for prediction of diabetic condition [73]. BCAA were associated with insulin resistance [74].



Figure 2: Metabolic pathway representing positive effects of arginine, alanine, leucine and glutamine in insulin secretion within pancreatic β -cell. (A) Alanine is converted to pyruvate which is then catalyzed by pyruvate dehydrogenase/pyruvate carboxylase to form Acetyl CoA or oxaloacetate. Leucine is catalyzed by amino transferase (AT) generating α -ketoisocaproate which is then catalyzed by branched chain ketoacid dehydrogenase (BCKDH) to form Acetyl CoA. Similarly, glutamine is converted to glutamate which is then catalyzed by glutamate dehydrogenase to form α -ketoglutarate. Acetyl CoA, oxaloacetate and α -ketoglutarate participate in TCA cycle generating ATP. The ATP produced *via* TCA cycle leads to membrane depolarization that facilitates Ca²⁺ influx which further helps in insulin secretion. L-Arginine causes membrane depolarization that allows calcium ion influx into the β -cells which mediates insulin receptor (containing tyrosine protein kinase) causes autophosphorylation which leads to activation of insulin receptor kinase. The insulin receptor binds to insulin receptor substrate 1 (IRS1) and phosphorylates it. Phosphorylated IRS1 binds to phosphoinositide-3-kinase (PI3K) which further phosphorylates phosphatidylinositol diphosphate (PIP2) to form phosphatidylinositol triphosphate (PIP3). PIP3 activates PIP3 dependent kinase which results in phosphorylation of protein kinase b (PKB/AKt). Akt inhibits tuberous sclerosis complex (TSC). This leads to activation of Ras homolog enriched in brain (Rheb). Rheb in turn activates mammalian target of rapamycin complex 1 (mTORC1). Activated mTORC1 further activates Ribosomal protein S6 kinase beta-1 (S6K1) which destabilizes IRS1 causing reduced insulin signaling. BCAA causes insulin resistance by directly activating mTORC1 through Heterodimeric RagGTPases.

In a randomized single blind cross over study comprising of 11 diabetic subjects, intake of whey proteins prior to meals was found to improve post prandial glycaemia and stimulate insulin secretion [75]. There are certain amino acids that are glucogenic such as alanine, glutamine, or glycine, histidine, arginine, and tryptophan which are not associated with insulin resistance; however, dietary branched chain amino acids and aromatic amino acids such as phenyl alanine and tyrosine do have association with insulin resistance [76]. Leucine, isoleucine and valine have branched aliphatic side chain. BCAA are useful in improving body composition. BCAA activates mammalian target of rapamycin complex 1 (mTORC1) by converting Rag to their active nucleotide bound form. Then, heterodimeric RagGTPases relocates mTORC1 to peri-nuclear region containing its activator Ras homolog enriched in brain (Rheb). Activated mTORC1 in turn activates Ribosomal protein S6 kinase beta-1 (S6K1) which phosphorylates and destabilizes Insulin receptor substrate 1 (IRS1) [77]. Thus, active mTORC1 inhibits insulin signaling for glucose uptake. However, the risk of T2DM due to BCAA intake depends on the dietary pattern [77].

Role of fats, fatty acids and cholesterol

The fatty acid metabolism in relation with diabetic condition has been depicted in Figure 3. Free fatty acids (FFA) in the plasma enter into the cells of the peripheral tissues. These fatty acids are converted into long-chain fatty acid acyl-CoA (LCFA CoA). Oxidation of LCFA CoA forms lipids which after lipolysis form diacylglycerol (DAG) and ceramide. Under hyperlipidemic condition, the excess of these metabolic derivatives hinder the insulin response signal cascade as depicted in Figure 3, causing insulin resistance.

The quality of the fat is more important than the quantity of the fat among diabetic populations. There is no mention of the amount of fat restriction among diabetic subjects. Saturated fatty acid (SFA) such as palmitic acid sequester the pancreatic and duodenal homeobox 1 (PDX-1) in the cytosol and reduces its nuclear localization thus reducing the GLUT2 expression. Consequently, failure to respond to extracellular glucose as well as inhibition of ER-Golgi protein trafficking by SFA leads to proinsulin buid-up in beta cells. SFA also cause proteolysis of carboxypeptidase E protein (CPE) that is involved in the biosynthesis of peptide hormones. These effects of SFA result in diminution of glucose stimulated insulin secretion. MUFA are considered beneficial for glucose control in T2DM [103]. MUFA block the enzyme caspase-3 that induces cellular apoptosis. MUFA also has antagonistic effect on the damage induced by saturated fatty acids (SFA). Inclusion of omega-3 fatty acids in the diet in diabetic people was found to be beneficial in preventing cardiovascular complications and maintaining renal function [104]. On the other hand, Omega-3-fatty acid binds with G protein coupled receptor 120 (GPR120) which leads to anti-inflammatory response by repressing macrophage induced tissue inflammation that includes inhibition of Interleukin-1 beta (IL-1β) and Toll-like receptor-4 (TLR-4) and enhancement in the insulin sensitivity [105,106]. GPR120 is a receptor of long chain unsaturated fatty acids and is abundantly expressed in adipose tissue, macrophages and intestine. Its function is considered as pivotal in management of diabetes as it enhances the overall insulin sensitivity. In adipocytes, binding of unsaturated fatty acid with GPR120 activates Gq/11 protein. Upon receiving the insulin, the insulin receptor



Figure 3: Sequential events in free fatty acid (FFA) mediated insulin resistance in skeletal muscle cell. Excess of FFA in plasma enters the muscle cell and gets converted into long-chain fatty acid acyl-CoA (LCFA CoA). LCFA CoA gets oxidized to form lipids which undergo lipolysis generating diacylglycerol (DAG) and ceramide. DAG and ceramide activates protein kinase C (PKC) which inturn activates kappaB kinase (IKK) and c-JUN NH2-terminal kinase (JNK). PKC, IKK and JNK stimulate serin-threonine phosphorylation which blocks tyrosine phosphorylation and dissociates phosphoinositide-3-kinase (P13K) from insulin receptor substrate (IRS1) while ceramide directly decreases Akt/protein kinase B (PKB) phosphorylation. Down-regulation of insulin signal cascade (from IRS1 to Akt)prevents GLUT4 translocation to membrane and hence glucose uptake is affected rendering the cell insulin resistant.



Figure 4: Graphical illustration representing sequence of events in amelioration of insulin resistance by polyunsaturated fatty acid (PUFA) under diabetic condition. Docosahexaenoic acid (DHA; 22:6n-3), an Omega-3-fatty acid in the plasma, is received by guanine nucleotidebinding regulatory (G) protein-coupled receptors, also called as the G protein-coupled receptor 120 (GPR120) or free fatty acid receptor 4 (FFAR4) in adipocytes. GPR120 functions as signaling molecule which activates heterodimeric G proteins (Gq/11). Gq/11 is then tyrosine phosphorylated by insulin receptor (IR) subsequently forming complex with p110α-subunit of phosphoinositide 3-kinase (PI3K). The activated PI3K is followed by signaling cascade involving phosphatidylinositol 4,5-bisphosphate (PIP2), phosphoinositide-3-kinase (PIP3), pyruvate dehydrogenase kinase 1 (PDK1) and protein kinase B (PKB) resulting in translocation of glucose transporter type 4 (GLUT4) to plasma membrane for glucose uptake, thus increasing insulin sensitivity. In macrophage cells, the toll-like receptors-4 (TLR4), functions as a signaling receptor for lipopolysaccharide (LPS) whereas, tumor necrosis factor receptor (TNFR) is a receptor for cell signaling cytokine, the tumor necrosis factor (TNF). TLR4 and TNFR initiate pro-inflammatory cascade by phosphorylating transforming growth factor β (TGF-β)-activated kinase 1 (TAK1). The binding of omega -3-fatty acid (ω-3 FA) with the receptor (GPR120) leads to subsequent association of the receptor with β-arrestin2. This is followed by internalization of both receptor and β-arrestin2 and their co-localization in the cytoplasmic compartment. This allows association of β-arrestin2 with (TGF-beta activated kinase 1 (MAP3K7) binding protein 1) which delinks TAB1 from TAK1. Due to this delinking, phosphorylation of TAK1 gets inhibited. Inhibition of TAK1 results in the blocking of inflammatory pathways such as inhibitor of nuclear factor kappa-B kinase subunit beta/ nuclear factor kappa-light-chain-enhancer of activated B cells (IKK\$/NFKB) and c-Jun N-terminal kinase/ Activator protein 1 (JNK/AP1) pathways ultimately leading to reduced insulin resistance.

associates with Gq/11 which then forms complex with phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K). A signaling cascade then follows leading to GLUT translocation for glucose uptake, thus enhancing insulin sensitivity as depicted in Figure 4. GPR120 is also involved in inhibition of macrophage induced tissue inflammation and reducing insulin resistance. Binding of omega-3-fatty acid stimulates GPR120. Then β-arrestin2 associates with the stimulated GPR120 which together participate in downstream signaling mechanism inhibiting lipopolysaccharides (LPS) and tumor necrosis factor (TNF- α) induced inflammatory signaling process as illustrated in Figure 4. When GPR120 is activated by unsaturated long chain fatty acids, it promotes the release of incretin glucagon-like peptide-1 (GLP-1) in gut enteroendocrine L-cells. GLP-1 is a polypeptide hormone which potentiates glucose stimulated insulin secretion, thus lowering the plasma glucose level. GLP-1 enables nutrient homeostasis in both pancreatic and extra pancreatic cells. In intestine, GLP-1 delays gastric emptying and sends signals of satiety to brain. In pancreas, GLP-1 promotes beta-cell differentiation, prevents its apoptosis and increases insulin secretion in glucose dependent manner by producing cyclic adenosine monophosphate (cAMP) [107]. GLP-1 reduces insulin resistance in pancreas, adipose, liver and muscle tissues. Particularly in hepatic and muscle cells, GLP-1 increases 5' adenosine monophosphate-activated protein kinase (AMPK) activity and fatty acid oxidation (Figure 5).

Plant stanols and sterols are beneficial in reducing LDL cholesterol in diabetic subjects. However, there are no reports on the effect of saturated fat, dietary cholesterol and transfat among diabetic populations. Cholesterol rich high fat diet tends to increase adipose tissue at various parts of body and activates innate immune system [108]. Generally, it has been shown that, such diet not only associated with obesity but also



Figure 5: Step-wise illustration of dietary cholesterol metabolism in T2DM. Dietary cholesterol is taken up by intestinal epithelial cells. Intracellular esterification of cholesterol by Acyl-CoA cholesterol acyltransferase (ACAT) forms cholesterol esters. Esterified cholesterol is grouped into chylomicrons which are transported to liver cells. Hepatic cholesterol forms very low density lipoproteins (VLDL) which are acted upon by lipoprotein lipase forming intermediate-density lipoprotein (IDL) and subsequently low density lipoprotein (LDL). Oxidized LDL enters beta cell through low density lipoprotein receptor (LDLR) by endocytosis. Under hypercholesterolemic condition, the liver X receptor (LXR) and ATP-binding cassette protein (ABCA1) gets inhibited which are responsible for efflux of cholesterol. The accumulated cholesterol leads to cellular stress followed by beta cell apoptosis and also activates neuronal nitric oxide synthase (nNOS). nNOS produces nitric oxide (NO) from L-arginine. NO production leads to s-nitrosylation of glucokinase and inhibits glucose-stimulated insulin secretion from pancreatic beta cells.

causes altered endocrine and metabolic regulations like diabetes, dyslipidemias, cardiovascular diseases, hepatic steatosis and cancer [109-116]. In case of T2DM, diet mediate increase of white adipose tissue and related immune response contributes to the cornerstone effect in disease pathology [108,112]. Association between diabetes mellitus and hypercholesterolemia, which is regarded as one of the most important factors involved in the acceleration of atherosclerosis in diabetic patients [117]. Researchers in this field have observed that plasma cholesterol levels in diabetic rats are notably high compared with non-diabetic animals [118]. Although there have been extensive studies on the catabolism of plasma lipoproteins in diabetic animals [119], only some have dealt with alterations in cholesterol absorption. The small intestine plays a key role in cholesterol metabolism because it is a site for the absorption of dietary cholesterol.

The pathway of cholesterol metabolism has been illustrated in Figure 6. Dietary cholesterol enters the mucosal cells in the form of unesterified sterol and is esterified before incorporation into chylomicrons and secretion to lymph. This esterification process is a regulatory factor in cholesterol absorption [120]. Two enzyme systems have been described for this esterification in the intestine. Early studies demonstrated that cholesterol esterase (EC 3.1.1.13) secreted from the pancreas penetrates into the intestinal absorptive cells and catalyzes cholesterol esterification through a reversal of the hydrolytic reaction [121]. Furthermore, several reports have indicated that acvl-CoA: cholesterol acyltransferase (ACAT, EC 2.3.1.26) are also important in controlling the transport of esterified cholesterol from the intestine [122]. An evident increment of plasma cholesterol levels with the accumulation of remnant lipoproteins in diabetic animals fed with a high-cholesterol diet ad libitum has been reported



Figure 6: Schematic representation of dietary fiber derived short chain fatty acids (SCFA) effects on glucose and insulin metabolism. Microbial fermentation of dietary fiber in colon yields SCFA which activates G-protein coupled receptors (GPR43 and GPR41). Subsequently, the Enteroendocrine L cells secrete gut hormones namely, glucagon like peptide (GLP-1) and pancreatic peptide YY (PYY). Various physiological effects of GLP-1 and PYY in different organs are illustrated. GLP-1 binds to G-protein coupled GLP-1 receptor in pancreatic islets allowing insulin gene expression, translation and proinsulin synthesis and insulin secretion. GLP-1 stimulates increased production of insulin and decrease in glucagon secretion thus promoting glucose uptake. In liver, SCFA decrease FA synthesis and promote FA oxidation. In adenosite tissue, SCFA promote secretion of leptin that suppresses apetite and increase expression of PPAR α genes involved in FFA oxidation leading to insulin sensitivity and glucose homeostasis. (†) mark indicates up-regulation and (4) mark indicates down regulation.

previously. The precise mechanism for diabetic hypercholesterolemia is unclear. Young et al. reported that hyperphagia in diabetes plays an important role in this phenomenon [123].

Accumulation of cholesterol with dietary fat acts as noxious stimuli and also held responsible for inflammation, an immune response which indicates activation of innate immune system [124]. Chemotactic cytokines or chemokines are released as an immediate response that attracts leucocytes and initiates leucocytes mediated defense orchestration [125]. It has been shown that minimally modified or oxidized LDL cholesterol activates toll-like receptors-4 (TLR-4), which is known to activate certain cytokines like tumor necrosis factor alpha (TNF α), macrophage inflammatory protein 2 (MIP-2), and monocyte chemo attractant protein 1 (MCP-1), initiates monocyte and macrophage accumulation and influences rapid process of inflammation [126]. LDL mediated immune activation and inflammation has not only been reported in T2DM but also in the case of atherosclerosis [127]. Experimental reports have shown that, inflammatory activation of TLR 3 or 4 leads to cholesterol accumulation in cell and in such cases Lipid X receptor (LXR)-ATP binding cassette protein A1 (ABCA1) complex are found inhibited and as a result, cholesterol efflux has been found clogged [127]. Cholesterol loaded cells are prone to cellular stress and related cellular toxicity [128]. Such cholesterol mediated cellular stress and apoptosis mediated cell death has been found in pancreatic β cells [129].

Some adipocyte derived cytokines (adipokines) has been found in altered levels during hypercholesterolemic diet induced inflammation, which are playing determining role in insulin resistance and T2DM [130,131]. Leptin, Adiponectin and Resistin are those molecules, having diversified functional contribution in T2DM [132,133]. During inflammatory processes, increasing levels of interleukins (IL-1, IL-6) and lipopolysaccharides (LPS) influences an uprising of leptin, indicating its protective potential against inflammatory response. Leptin also modulate the activity of T-cells and thereby potentiates the protective pathway [134]. Adiponectin is crucial most adipokine, having multiple functional contributions in the pathology of T2DM. It increases fatty acid oxidation, decreases glucose synthesis in the liver and also involved in the feedback sensitivity of insulin receptor and thereby shows protective aids against insulin resistance either through modulating transcription factor, like peroxisome proliferator-activated receptor α (PPAR α) or *via* LPS activation [132,133]. Resistin, another adipokine found in increasing levels in inflammatory state is associated with positive feedback system. It also plays an important role in insulin resistance and cardiovascular dysfunction [135,136].

The formation of lipid rafts-cholesterol enriched microdomains of plasma membrane is promoted by accumulation of membrane cholesterol [137]. High cholesterol concentration of media causes accumulation of excess cholesterol in membrane in mouse insulinoma (MIN6) cells. High cholesterol induced formation of lipid rafts resulted in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation mediated generation of reactive oxygen species (ROS) has been suggested to be the reason of LDLs loading induced apoptosis of MIN6 cells. Lipid raft clustering is stimulated by the death receptor ligands and apoptotic factors resulted in activation of NADPH oxidase and consequent cellular dysfunction [138]. It is also suggested that the LDLs loading induced apoptosis of MIN6 cells is due to promoted formation of lipid raft, resulted in the activation of NADPH oxidase and hence generation of ROS [139]. However, reduction of membrane cholesterol impedes insulin secretion due to association of ion channels and soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins with the rafts in β -cells [140].

Role of carbohydrates

The source of carbohydrates is being considered as more important than the quantity for management of diabetes. Carbohydrates from fruits, vegetables, whole grains are considered more beneficial in the management of diabetes than refined carbohydrates. Fructose intake from naturally occurring foods or fruits is considered good for blood glucose management than isocaloric sucrose or starch. The property of increased viscosity and gel formation due to the presence of soluble fiber reduces the bioavailability of macronutrients and thus reduces post prandial blood glucose level. Prospective cohort studies have emphasized that insoluble dietary fiber (IDF) from cereals and whole grains is consistently associated with reduction in risk of diabetes rather than soluble dietary fiber (SDF) [141]. In whole grain sorghum flour, the IDF content was 25% and the corresponding GI was 77 (Table 2). In water melon even though the IDF was comparatively lesser, the GI was 76 because of higher GL. Coconut flour with less than 55 GI was found to contain 0.3% of SDF. Based on 31,641 participants, it was observed that intake of carbohydrates and magnesium was negatively associated with incidence of diabetes whereas, dietary GI and diabetes were positively associated with starch intake [142]. However, Makris et al. have observed that there was no effect of either protein or GI or their interaction effect on glucose or insulin response in overweight adults [143].

IDF improves insulin sensitivity and reduced diabetes risk. Intake of high levels of dietary fiber was linked decreased risk of mortality among diabetic population and particularly among diabetic people with normal weight; higher sugar intake was associated with high mortality risk [54]. Total dietary fiber is inversely associated with insulin resistance. Microbial fermentation of dietary fiber in the colon produces short chain fatty acids (SCFA) such as acetate, propionate and butyrate which reduce hepatic glucose output. SCFA such as propionic acid reduces hepatic gluconeogenesis and stimulates glycolysis. The positive and beneficial effects of SCFAs in T2DM have been schematically represented in Figure 5. SCFAs activate free fatty acid receptor (FFAR2). FFAR2 couples to both the Gq and Gi/o pathway leading to influx of Ca²⁺ ions. This leads to the production of glucagon like peptide (GLP-1) by enteroendocrine L cells. GLP-1 binds to G-protein coupled receptor resulting in the activation of adenylate cyclase. Subsequently cyclic adenoside monophosphate (cAMP) gets enhanced leading to intracellular signaling ultimately resulting in insulin secretion.

Role of micronutrients

Chromium is present in the form of CrCl₂ in various food sources at microgram level (Table 1). Vegetables such as broccoli and whole cereals are rich sources of chromium. Cefalu et al. have conducted an elaborated review on the effect of chromium on blood glucose and found that chromium reduces blood glucose level, HbA1c and improves insulin sensitivity [21]. Suksomboon et al. also observed that chromium supplementation reduced the HbA1c [144]. Iron is an essential micronutrient which occurs in cereal grains and green leafy vegetables. It has positive effects on beta cell functioning and reduction of inflammatory response. Magnesium is important for insulin sensitivity since it is a cofactor in more than 200 metabolic reactions and is an important metalloenzyme in phosphorylation and dephosphorylation reactions in glycolysis. Green leafy vegetables, cereals and legumes are rich sources of magnesium (Table 2). Akter et al. have reported that dietary magnesium rather than serum magnesium concentration was negatively correlated with homeostatic model assessment of insulin resistance in healthy adults [145]. Protein kinase in insulin signaling cascade and secretion of insulin is dependent on magnesium. In the present review, it was observed that barley, containing 79 mg/100 g of magnesium, exhibited GI of 28 which can be considered as low (Table 2). Biotin functions as a coenzyme bicarbonate dependent reactions, modulates in glucokinase activity and suppresses gluconeogenesis by limiting phosphoenolpyruvate carboxykinase. Biotin was found to be densely distributed in brown rice, barley and banana among which barley was found to elicit least GI of 28 (Table 2). In combination with chromium, biotin reduces fasting glucose level, HbA1c, cholesterol and LDL [146,147]. Hong et al. studied the interaction of variants of insulin resistant genes with the nutrients and found that T2DM risk was higher in subjects with high energy and low calcium intake [148]. Myers et al. studied the implications of zinc and insulin signaling on T2DM [149]. Zn is a component in zinc transporter-8 (ZNT8) which is predominantly present in beta-cells of the pancreas which transports zinc into insulin secretory granules [150,151]. Other transporters such as ZIP6 and ZIP7 also have zinc that control insulin signaling [152,153].

Vitamin E intake has beneficial effect on T2DM as it was associated with alleviation of oxidative stress in pancreatic β -cells [154]. Xu et al. have observed that there are no substantial evidences to prove that supplementation of vitamin E causes improvement in HbA1c and fasting blood glucose level in T2DM subjects [155]. In the present review, highest content of vitamin E was found to be in pumpkin seed oil followed by brown rice (Table 2). Vitamin C occurs densely in citrus fruits is helpful in insulin secretion by virtue of its antioxidative effect [156,157]. Vitamin C has the potential to reduce triglycerides. In a study conducted on 42 healthy subjects, Sur et al. have observed that vitamin D level was negatively associated with fasting blood sugar and postulated that hypovitaminosis of vitamin D may lead to T2DM [158]. Based on observational cohort studies and randomized controlled trials, Mitri et al. have observed that individuals with higher vitamin D status are less prone to development of T2DM [159]. The vitamin D content of chickpea was found to be as high as 1.93 mcg/100 g with corresponding GI of chick pea being 28 (Table 2). The GI and starch intake were inversely related to intake of micronutrients and lower GI was one of the predictors for desirable micronutrient profile among pregnant women [55].

Bioactive compounds and phytochemicals

Dietary bioactive components have important role in the basic human metabolism and also in disease condition. These components exert their influence by virtue of their unique structural configuration and interaction with bio-molecules. Dietary components with bioactive properties act against the manifestation and progression of disease/disorder confers improvement in health outcomes and stabilizes basic metabolism [160,161]. Bioactive components are beneficial and effective in several chronic disease conditions with their modulatory effect on dysregulated metabolic pathways which are highly relevant to disease progression and treatment. The increased preference for and recent focus on biologically sourced active components is because they can be consumed over a prolonged period of time devoid of any adverse side effects and can be easily accessed

from dietary resources by vulnerable population. Intake of dietary bioactive components lessens the burden of medication especially in chronic disease conditions such as diabetes where there is no definitive medication course for a permanent cure and the medication needs to be continued life-long.

Phytic acid (inositol hexakisphosphate), a cyclic acid, is the main storage form of phosphorus in seeds. The salt form of phytic acid is termed as phytate. Phytic acid occurs mostly in cereal grains, nuts and legumes. Among cereals and millets, the phytic acid content ranges from 0.06 g to 7.3 g/100 g on dry weight basis [162]. Almond is one of the rich sources of phytic acid containing as high as 9.42 g/100 g on dry weight basis. Among legumes, its content ranges from 0.22 to 2.38 g/100 g (Table 1). It functions as a strong chelating agent for divalent cations and consequently has the potential to limit the bioavailability of metabolically important minerals such as iron, zinc and calcium. Some of the divalent cations are cofactors of enzymes and transporter proteins of glucose. Phytic acid also chelates calcium which is the cofactor in the enzyme alpha amylase thus inhibiting its activity and reducing glycaemic propensity. Therefore, phytic acid indirectly acts on glucose metabolism by inhibiting synthesis and glucose uptake. Phytic acid also binds with starch and starch associated proteins thus hindering their digestion and exerting glycaemic control [14]. When phytic acid was fed to chemically induced T2DM rats at the rate of 650 mg/kg for 28 days, it was found that the glucose level and HbA1c have in fact decreased. A dose dependent inhibition of alpha glucosidase and reduction of alpha amylase activity was found. Therefore, phytate helps in lowering blood glucose level either by binding with glucose releasing starch or by inhibiting the enzymes involved in starch digestion. This is additionally corroborated by the fact that among 15 different food sources, the phytic acid content was significantly and negatively correlated (r=-0.8; $P \le 0.05$) to their respective glycaemic indices. Yoon et al. also observed that sodium phytate at the rate of 2% of starch portion reduced *in vitro* digestion by 50% [163]. Therefore, phytic acid has immense potential in regulation of glycaemic condition. In this review, it was found that barley having phytic acid content of 386 mg/100 g elicited a GI of 28 whereas kidney beans containing upto 481 mg/100 g of phytic acid could elicit a GI of 24 (Table 2). Both these food sources can be considered as low GI foods.

Some of the rich dietary source of glycine betaine includes spinach, whole wheat, and marine invertebrates [164]. Betaine functions as intracellular osmolyte. Betaine exhibits a protective effect on the pancreatic beta cells from excess of glucose molecules in the blood stream in the diabetic condition (Table 1). Increased level of betaine was previously found to be associated with higher insulin sensitivity and lower risk factors of diabetes such as triglycerides and adiposity (Figure 7). Betaine was also found to be effective in normalization



Figure 7: Promoting and inhibitory effect of nutrients on diabetic features *viz.*, (1) Blood glucose/Glycaemic index (2) Glycated Haemoglobin (HbA1c) (3) Insulin resistance and (4) Insulin secretion. Down arrow (1) represents inhibitory effect while up-arrow (1) represents promoting effect of the nutritional components on the corresponding diabetic features. Interrelation among diabetic features with T2DM was linked by connecting arrows.

of gluconeogenesis and glycogenolysis in HepG2 cells. Lever et al. have observed that enhanced level of betaine metabolite, an analog- trimethylamine-N-oxide (TMAO) is a strong risk factor in diabetes [165]. Tiihonen et al. have reported that betaine has good bioavailability among Asian populations and was effective in improving the liver metabolism [166]. Lever et al. have reported that the plasma concentration of glycine betaine was not correlated to glycosylated haemoglobin, however, renal excretion was highly significant among diabetic patients [167]. On the contrary, Dellow et al. reported that excretion of betaine was significantly correlated with plasma glucose and glycated haemoglobin [168].

Morin is a natural biflavonoid compound that has anti-diabetic property; however, most of the reports

pertain to *in vitro* or animal model studies [169]. Recent studies show that morin has anti-oxidative capacity in rat pancreatic beta cells and regulates carbohydrate metabolic enzyme activities [170,171]. Seyyedebrahimi et al. have demonstrated that supplementation of resveratrol at the rate of 800 mg/day showed antioxidative effect in T2DM patients in a randomized, double blind, placebo controlled clinical trial [172]. Berberine, curcumin, salidroside and cryptotanshinone have been reported to exert AMPK mediated promotive effect on glucose uptake by muscle and adipose tissue while fiber fractions from rice bran showed glycaemic control [62]. In a recent review, resveratrol has been reported to improve metabolic functioning in T2DM patients [173]. Tannic acid has been shown to have inhibitory effect on alpha glucosidase enzyme activity by hydrophobic and electrostatic interaction with them [174].

Arabinoxylans are non-starch polysaccharides which occur in cereals. Structurally, it is an arabinofuranosyl substituted polymer of xylose. Intake of arabinoxylan has been associated with lower level of serum glucose particularly in impaired glucose tolerance condition [175] and metabolic control of blood glucose in people with T2DM [176]. Arabinoxylans limits access to enzymes and impedes absorption of glucose in the small intestine (Table 1). The water extracts of arabinoxylan from wheat bran and aleurone layers have shown antiglycaemic properties due to inhibition of alpha glucosidase activity [177]. Arabinoxylan stimulates SCFA production such as butyrate and acetate [178]. SCFA decrease gluconeogenesis in liver thus controlling blood sugar level (Figure 7). Clinical trials have shown that consumption of arabinoxylan crackers have shown beneficial effect on glycaemic control among overweight subjects [179]. Lu et al. [176] have demonstrated that supplementation of arabinoxylan rich fiber at the rate of 15 g per day significantly improves glycaemic control in T2DM. Based on human trials, it was established that long term intake of long chain arabinoxylans has the potential to reinstate glucose and insulin metabolic functions in T2DM patients [180]. Similarly beta-glucan was also found to improve insulin sensitivity. Among the cereals containing arabinoxylan, lowest GI of 29 was observed for rye (Table 2).

Alkylresorcinols are phenolic lipids that are catabolized in the liver into two different metabolites. Sun et al. have reported that plasma alkylresorcinol metabolite 3-(3,5-dihydroxyphenyl)-1-propanoic acid (DHPPA) level was inversely associated with T2DM and impaired glucose metabolism among Chinese people [181]. Alkylresorcinols have the capacity to bind to alpha amylase and alpha glucosidase thus limiting their activity. Biskup et al. have studied the plasma alkylresorcinol association with risk of T2DM and observed that consumption of whole grains composed of substantial amount of rye is associated with lower risk of T2DM among Scandinavian population [182] and alkylresorcinols metabolites in plasma are proportional to rye fiber intake [183].

Lectins or haemaglutinins are a large group of proteins with the ability to bind to carbohydrates without changing their structures [184]. Lectins can be one of the potential causes for instigation of insulin dependent diabetes [185]. In this review, it was noted that soy beans and chick peas containing 87 HU/mg and 180 HU/ mg of lectins could elicit GI of 15 and 36, respectively, which were comparatively lower than GI values elicited by either wheat, potato or banana that contain lesser concentration of lectins ranging from 1.3 HU/mg to 13 HU/mg (Table 2). Guan et al. have observed that mannose binding lectins (MBL) were elevated in T2DM patients with nephropathy and suggested its role in the pathogenesis [186]. MBL has also been associated with pathogenesis of vascular complications in T2DM [187].

Alkylresorcinols, lectins and phytic acid are able to bind to α -amylase (an enzyme involved in starch digestion), limiting its activity. Another enzyme involved in carbohydrate digestion is α -glucosidase, which can be inhibited by phenolic acids and alkylresorcinols. Absorption of glucose from the intestines to the bloodstream goes through sodium dependent glucose transporter (SGLT1) localized in the intestinal brush border membrane. Ferulic and chlorogenic acids exhibit an ability to block this transporter, limiting the rate of absorption. Therefore, phenolic acids are important in the modulation of glucose uptake from blood to muscle cells (Table 1). Triterpene acid, generally found in medicinal plants was also found to have improving effect on T2DM [28].

On an overall basis, the nutritional components derived from different food sources executes their physiological functions in a manner that regulate the glycaemic effects in terms of blood glucose level (GI), glycated haemoglobin level, Insulin secretion and Insulin resistance. A large number of nutrients, comprising of gross nutrients such as dietary fiber, proteins, carbohydrates and fats, were implicated directly in regulation of blood glucose level and comparatively fewer numbers of nutrients, mostly comprising of bioactive components and amino acids, were associated directly with insulin metabolism that includes insulin resistance and sensitivity (Figure 7). Therefore, it can be suggested that diets rich in bioactive components are highly relevant for prevention and alleviation of chronic T2DM while a most optimal combination of carbohydrate, fat and protein can be chosen as a diet for symptomatic reduction of hyperglycaemia.

CONCLUSIONS

After digestion by the action of gastric enzymes, the food matrix along with glucose and several nutritional components are absorbed into the blood stream. These components have different effects on the glucose level as well as insulin secretion and functioning. Protein and fat metabolism were found to have a strong association with glucose and insulin metabolism and act in synergy to regulate and maintain optimal blood glucose level. This review collates the scientific information of several nutrients that have been identified and characterized for their influence on glycaemic regulation. Additionally, their individual and synergistic roles in human metabolism as well as their site of action can be interpreted. Some of the nutrients such as dietary fiber and available carbohydrates act on a dose dependent manner at the bio-accessibility level on the glucose release rate. Micronutrients and bioactive components exert their influence on the blood glucose release, insulin metabolism and action at the metabolic level. Nutrients such as fatty acids, vitamin D, potassium, sodium and glucose play an important role in nutrigenomics. However, foods contain a wide spectrum of nutrients and bioactive compounds that have individual or synergistic influence on human physiology. It can be seen that only a very less percentage of those nutrients have been studied in terms of their glycaemic regulatory effects. Even though certain under reported nutrients such as morin and resveratrol have been mentioned in this review, further studies are required for deciphering the implication of such nutritional components in manifestation of risk factors of diabetes. This review also forms foundation for evaluating the genetic and epigenetic changes associated with different types of diabetic conditions from nutrition angle. The genomic and metabolomics aspects comprising of the receptors and/or targets can be discussed in our further review based communications. It was observed that only few clinical trials were conducted on nutraceutical components and greater emphasis need to be laid on such investigations.

ABBREVIATIONS

ACAT: Acyltransferase; ADA: American Diabetes Association; ADP: Adenosine Diphosphate; AHEI: Alternate Health Eating Index; AMPK: 5' Adenosine Monophosphate-Activated Protein Kinase; AT: Amino Transferase; ATP: Adenosine Triphosphate; BCAA: Branched Chain Amino Acids; BMI: Body Mass Index; cAMP: Cyclic Adenosine Monophosphate; CDC: Centers for Disease Control and Prevention; CPE: Carboxypeptidase E Protein; DAG: Diacylglycerol; DPP-IV: Dipeptidyl Aminopeptidase IV; FAO: Food and Agriculture Organization; FFA: Free Fatty Acids; FPG: Fasting Plasma Glucose; GDH: Glutamate Dehydrogenase; GDM: Gestational Diabetes Mellitus; GI: Glycaemic Index; GLP-1: Glucagon-Like Peptide-1; GLUT: Glucose Transporter Protein; GPR120: G Protein Coupled Receptor 120; HbA1c: Glycated Haemoglobin; HNF1A: Hepatocyte Nuclear Factor 1 Alpha; IGT: Impaired Glucose Tolerance; KATP: ATP Sensitive Potassium Channel; LCFA CoA: Long-Chain Fatty Acid Acyl-CoA; mTORC1: Mammalian Target of Rapamycin Complex 1; MUFA: Monounsaturated Fatty Acids; OGTT: Oral Glucose Tolerance Test; PDX-1: Pancreatic and Duodenal Homeobox 1; S6K1: Ribosomal Protein S6 Kinase Beta-1; SFA: Saturated Fatty Acid; T2DM: Type 2 Diabetes Mellitus; VGCC: Voltage Gated Calcium Channel; WHO: World Health Organization; MIP-2: Macrophage Inflammatory Protein 2; MCP-1: Monocyte Chemo Attractant Protein 1; LXR: Lipid X Receptor; ABCA1: ATP Binding Cassette Protein A1; PPARα: Peroxisome Proliferator-Activated Receptor α; NADPH: Nicotinamide Adenine and Dinucleotide Phosphate; ROS: Reactive Oxygen Species; SNARE : N-ethylmaleimide-Sensitive Factor Attachment Protein Receptor; SCFA: Short Chain Fatty Acids; FFAR2: Free Fatty Acid Receptor; GLP-1: Glucagon Like Peptide; ZNT: Zinc Transporter; TMAO: Trimethylamine-N-Oxide

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

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