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Review on the Mechanism of Diabesity: In-vitro and In-vivo Methods of Evaluations

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Abstract

Mechanism of diabesity is modulated by adiposity and visceral fat deposits which is link to insulin resistance mediate mechanisms. The action of obesity and diabetes are attributed to insulin resistance resulting from visceral adiposity and their differential distribution in tissues, endoplasmic reticulum stress. Randle theory of glucose fatty acid substrate competition are the mechanistic causes of obesity while pancreatic enzyme inhibition and triglycerides absorption and impaired carbohydrates, protein and fat metabolism are attributed to diabetes regulations. In-vivo obesity methods of evaluation were anthropometrically based Densitometry method, plathysmography, magnetic resonance, computational tomography and Dixon methods amongst others were outlined as obese measuring tools. In-vitro methods include; Dual-energy absorptiometry, plurality of polymorphic genes and metreleptin approaches. In-vitro model for diabetes evaluation were based on activity of pancreatic enzymes derivatives. Hemoglobin calculation test. Other includes; animal model test such as monosodium glutamate test, growth hormone test and spontaneous diabetes rats test as *In-vivo* approaches to diabetes measurements. Molecular dietary nutrition could help tailor these matrixes of glucose level mediation within and about cells in obesity and diabetes epigenesis.

Keywords: ***Diabesity; Mechanism; Methods; Obesity; Diabetes; Evaluation***

1. Introduction

Diabesity is a term that refers to the complicated conditions of diabetes and obesity occurring simultaneously within a single individual however it is also associated with lifestyle and dietary habits, aside from genetic vulnerability. Diabesity is a patho physiological link between diabetes and obesity- adiposity and visceral fats linked to insulin resistance as risk factors [1] Obesity and diabetes are disorders arising primarily from nutritional disease or conditions necessitated by dietary patterns found in individuals, community and nations. Over one hundredth and fifty (150 million) people are suffering from obesity and

diabetes and are disposed to these conditions, hence graduating from epidemic to pandemic situations [2]. Obesity is a heterogeneous disorder associated with accumulation of excessive body fat, resulting in a pathway in which energy intake chronically exceeds energy expenditure [3,4]. Excessive weight gain resulting from certain eating habits which is primarily influenced by peer pressure, sedentary activities and consuming large portions of food and sugar containing foods [5].

Prospective epidemiological studies have revealed that central obesity determined by waist circumference and Waist Hip Ratio are more relevant in CAD risk compared to general obesity determined by BMI [6] while Waist Hip Ratio is commonly used in reflecting central obesity. Waist circumference is shown to have a better correlation with abdominal fat localization Recent data indicate that in USA, less than 9.1% of the age adjusted population had diabetes in 2014 and additional 86 million adults had pre-diabetes. There are two major classifications of diabetes mellitus, type 1 diabetes mellitus (T1DM) is associated with complete or near-total insulin deficiency of pancreatic cells. This result in hyperglycaemia sugar increase in the blood which could results in micro vascular (retinopathy, nephropathy, neuropathy and macro vascular diseases (coronary arterial disease, peripheral vascular disease, stroke and renal failure). T2DM is associated with variable degrees of insulin resistance, impaired insulin secretion resulting in severe cell apoptosis in the pancreas, and increased hepatic glucose production. Lifestyle changes, dietary factors are modulators of incidences of diabetes and in the management of diabetes. This review seeks to establish and create awareness on the methods and molecular mechanism of obesity and diabetes, a hidden epidemic in developed and developing countries.

1.1 Diabesity

The condition of ‘diabesity’ is a comparatively newer terminology associated with the interrelationship between diabetes and obesity. The condition is also infused to be a patho-physiological link associating obesity and diabetes, being characterized as a serious gradual public health issue [1]. Diabesity refers to the complicated conditions of diabetes and obesity occurring simultaneously within a single individual [1]. The incidences of diabetes and obesity are growing at a rapid pace throughout the world that is mainly associated with lifestyle and dietary habits, aside from genetic vulnerability. Authors have reviewed the epidemiology and other negative aspects of diabesity followed by some of the management practices recommended.

The declining of traditional lifestyles and dietary patterns is leading to a rapid increase in the prevalence of diabesity that is upcoming as a serious cause of concern world over. Diabetes, obesity, and their associated complications are without doubt a principal issue and threat in developing and under-developed nations. Diabesity has emerged as a major threat in developed nations. This condition has been described as a slow poison, whose influence cannot be controlled or cured.

1.2 Obesity

Obesity has been proven to be an independent risk factor for coronary artery disease (CAD) in both genders [7]. Bodyweight, body mass index (BMI), waist circumference and waist-hip ratio (WHR) are primary methods to determine obesity while BMI reflects general obesity. Waist circumference and waist-hip ratio are related to central-type obesity where body fat is primarily located in the abdomen [8]. Prospective epidemiological studies have revealed that central obesity determined by waist circumference and (WHR) is more relevant in CAD risk compared to general obesity determined by BMI [9] while WHR is commonly used in reflecting central obesity. Waist circumference is shown to have a better correlation with abdominal fat localization.

1.3 Diabetes

Diabetes is directly related to insulin production from the pancreas. Insulin, a hormone from the pancreas that regulates the metabolism of sugar. Sometimes the released insulin from β cells of islet of Langerhans in the pancreas may not be sufficient enough and other times may not be able to regulate excess glucose in the blood. The insulin release irregularity tendency results in type 1 and type 2 diabetes.

1.4 Type 1-diabetes

This occurs when the body fails to produce enough insulin. It is an autoimmune disorder or disease condition that destroys the β cell of the pancreas leading to insulin deficiency in the blood. This results in hyperglycaemia, sugar increase in the blood which could result in micro vascular such as retinopathy, nephropathy and neuropathy and macro vascular diseases such as coronary arterial disease, peripheral vascular disease, stroke and renal failure.

1.5 Type 2-diabetes

When the body fails to responds to insulin in a normal way, it's either the insulin is not activated or over metabolising blood sugar resulting in hyperglycemia. The in-responses of insulin create insulin resistance which results in hyperglycemia and these occur usually in adults. The net result of insulin resistance is compensatory hyperinsulinemia. Afterword, the β -cell s of the pancreas fails to meet the compensatory needs and results in less insulin secretion required for metabolism of glucose giving way to hyperglycemia, dyslipidemia and hypertension which are common triggers of type 2 diabetes.

According to Eze NM and Njoku HD [4], the precursor to type 2 diabetes is obesity and tends to increase as aging sets in. Fasting sugar level of 140-126 mg/l, diagnostic criteria of 110-126 mg/l and by impaired glucose tolerance of ≥ 126 are the major parametric measures of diabetes in patients.

1.6 Gestational or type III diabetes

This kind is associated with pregnancy and commonly seen in pregnant women when carbohydrate intolerance is noticed first or glucose level is noticed first in pregnant women. Some women have very high levels of glucose in their blood and their bodies are unable to produce enough insulin to transport all of the glucose into their cells, resulting in progressively rising levels of glucose. Diagnosis of gestational diabetes is made during pregnancy [10].

1.7 Pre-diabetes

The vast majority of patients with type 2 diabetes initially had pre-diabetes. Their blood glucose levels where higher than normal, but not high enough to merit a diabetes diagnosis. The cells in the body are becoming resistant to insulin. Studies have indicated that even at the pre-diabetes stage, some damage to the circulatory system and the heart may already have occurred FIG. 1 [11].

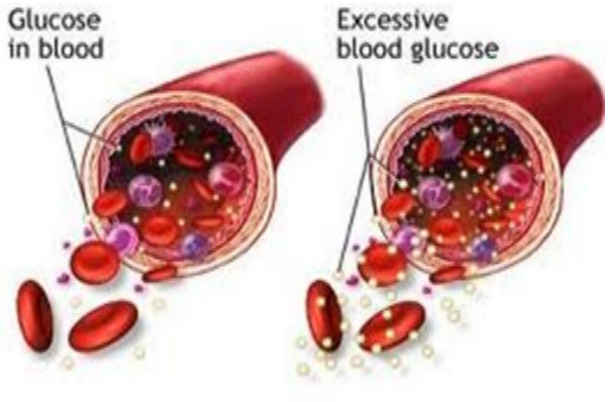


FIG. 1. **Excess glucose presence in the blood.**

1.8 Insulin physiology and metabolic regulation

Hepatocytes, skeletal myocytes, and white adipocytes are regarded as classic insulin-responsive tissues. Most cells express surface insulin receptors. Insulin regulates glucose metabolism both through direct actions and in part by influencing inter organ cross talk pathways including the synthesis and secretion of fat-derived adipocytokines. Insulin signaling in the brain influences energy balance and peripheral glucose metabolism [9]. Other non-classic target tissues for insulin include the heart, skeleton [12,13], brown adipocytes and ovaries [13,14]. The metabolic function of these organs may be favourably or unfavourably affected by insulin-sensitizing drugs [11]. The range of physiological actions of insulin has expanded beyond regulation of carbohydrates and other macronutrients to include antioxidant, anti-inflammatory and vascular effects [15]. Cellular Insulin signaling in peripheral tissues. For example, muscle and fat. Insulin must leave the intravascular compartment and traverse the interstitial space before interacting with cellular insulin receptors [16]. The insulin receptor is a transmembrane heterodimer comprising two α- and two β-subunits binding to the α-subunit inducing a conformational change resulting in release of the inhibitory effect of the α-subunit and autophosphorylation of tyrosine residues in the β-subunit [17]. Insulin receptor tyrosine kinase phosphorylates and recruits substrate adaptors such as the insulin receptor substrate (IRS), a family of proteins. This initiates molecular events that result in translocation of the facilitative glucose transporter (GLUT4) from the cytosolic vesicles to the cell membrane [18]. Fusion of GLUT4 with the cell membrane transports glucose into the cell where it is phosphorylated to glucose-6-phosphate. A post-binding cascade of phosphorylation/ dephosphorylation reactions [19].

This leads to activation of key enzymes including glycogen synthase and pyruvate dehydrogenase. In the presence of hyperinsulinaemia, glucose-6-phosphate is mainly (approximately 70%) polymerized to form glycogen; the remainder enters the glycolytic pathway and is either oxidized or converted to lactate. Insulin is a potent growth factor that exerts transcriptional effects on cell growth and differentiation [20], via the mitogen-activated protein (MAP) kinase pathway. Other actions of insulin include regulation of protein metabolism and aspects of cellular ion transport.

1.9 Obesity and type 1 diabetes

The “accelerator hypothesis” proposed by Kahn SE [21] had demonstrates the association between body mass and type 1 diabetes in young age groups. This is explained by the fact that more weight accelerates insulin resistance, leading to the development of type 1 diabetes in individuals who are predisposed genetically to diabetes. Other factors such as presence or

absence of breast milk feeding, exposure to cow milk feeding of babies, exposure to certain infection, overfeeding and hormonal dysregulations has been associated with type 1 diabetes. However, the exact mechanism and relationship between type 1 diabetes and obesity remains inconclusive and needs further explanation [21].

1.10 Obesity and type 2 diabetes.

Obesity is linked to many medical, psychological, and social conditions, the most devastating of which may be type 2 diabetes. Both type 2 diabetes and obesity are associated with insulin resistance. Throughout the natural history of type 2 diabetes, endothelial dysfunction is accompanied with obesity/insulin resistance in diabetes and prediabetes conditions. Developing insulin resistance and obesity, comes from β-cells not able to compensate fully for decreased insulin sensitivity. The nonesterified fatty acids (NEFAs) that are secreted from adipose tissue in obese people may lead to the Randle hypothesis that insulin resistance and β-cell dysfunction are most likely linked [22].

1.11 Obesity and insulin resistance

Insulin sensitivity fluctuation occurs across the natural life cycle. lifestyle variations, such as increased carbohydrate intake and decreased physical activity, are associated with insulin sensitivity fluctuations, [23,24]. Obesity is considered the most important factor in the development of metabolic diseases. Adipose tissue affects metabolism by secreting hormones, glycerol, and other substances including leptin, cytokines, adiponectin, and pro-inflammatory substances, and by releasing NEFAs. In obese individuals, the secretion of these substances will be increased (FIG. 2).

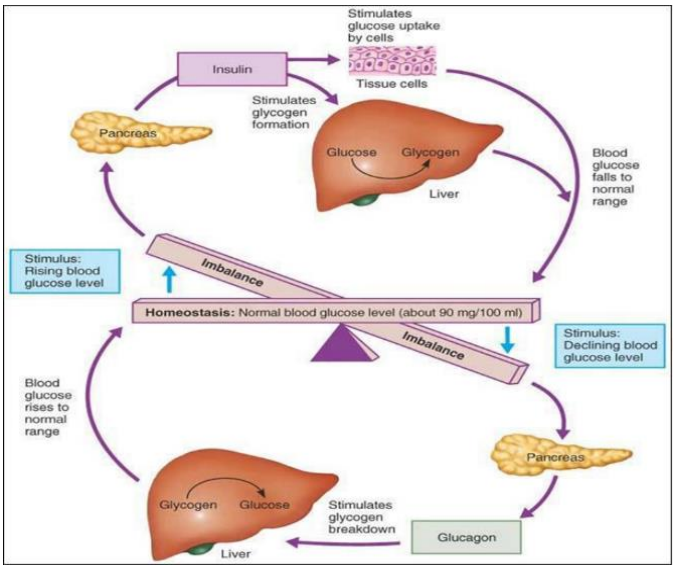


FIG. 2. **Blood glucose level maintenance in the body.**

2. Mechanism of Obesity and Diabetes

2.1 Insulin resistance

Insulin resistance (IR) is manifested by reducing the ability of insulin to activate the insulin signaling pathway. At the molecular level, IR is characterized by diverse alterations in various intracellular signaling pathways. In fact, it has been shown that insulin signaling is impaired in the liver, muscle, adipose tissue, hypothalamus, and others tissues, in IR states. While there are

several biological events that can lead to the impairment of the insulin signaling pathway, chronic inflammation is perhaps the best described. Several factors have been proposed to explain the mechanisms of insulin resistance. These include: (a) obesity; (b) inflammation; (c) mitochondrial dysfunction; (d) hyperinsulinemia; (e) lipotoxicity/hyperlipidemia; (f) genetic background; (g) endoplasmic reticulum stress; (h) aging; (i) oxidative stress; (j) fatty liver; (k) hypoxia; (l) lipodystrophy; (m) pregnancy. Although the primary factors causing this disease are unknown, it is clear that insulin resistance plays a major role in its development.

Insulin resistance may be defined as a state in which physiological concentrations of insulin produce a less than normal biological response [22]. Visceral adiposity, which is often accompanied by chronic low-grade systemic inflammation and alterations in cytokine physiology, is more closely associated with insulin resistance and risk factors for cardiometabolic diseases. Insulin resistance is attributed to differential distribution of adipose tissue. Insulin resistance (IR) is manifested by reducing the ability of insulin to activate the insulin signaling pathway. At the molecular level, IR is characterized by diverse alterations in various intracellular signaling pathways such as Endoplasmic reticulum stress ER characterized by unfolded and folded protein, activates and amplify inflammatory signals and insulin resistance in responses to obesity induced metabolic disturbance. It has been shown that insulin signaling is impaired in the liver, muscle, adipose tissue, hypothalamus, and others tissues, in IR states. While there are several biological events that can lead to the impairment of the insulin signaling pathway, chronic inflammation is perhaps the best described. Several factors have been proposed to explain the mechanisms of insulin resistance. These include: obesity, inflammation, mitochondrial dysfunction, hyperinsulinemia, lipotoxicity/ hyperlipidemia, genetic background, endoplasmic reticulum stress, aging, oxidative stress, fatty liver, hypoxia, lipodystrophy and pregnancy. Although the primary factors causing this disease are unknown, it is clear that insulin resistance plays a major role in its development (FIG. 3).

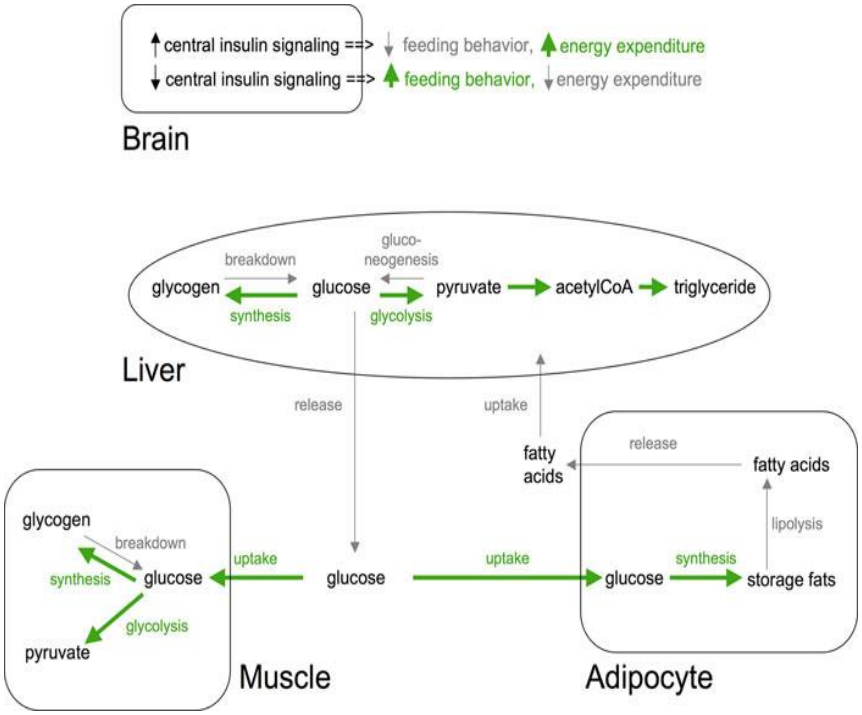


FIG. 3. **Mechanisms linking glucose to T2D risk.**

Lipotoxicity theory' that proposes a probable metabolic model by which prolonged fat excess is positively correlated with both insulin resistance and decreased insulin secretory capacity of beta cells, in the context of concomitant hyperglycaemia.

3. Mechanism of Obesity

Adipose tissue is an endocrine active organ that secretes bioactive polypeptides called adipokines. Adipokines acts centrally to regulate appetite and energy expenditure and peripherally affects insulin oxidative capacity and lipid uptake. The adipokines profile changes responding to the amount and condition of adipose tissue and in obesity. The imbalance release of these molecules leads to metabolic disturbance that play a central role in the development of additive disease in obese condition. One area of potential importance in the pathogenesis of insulin resistance in obesity is glucose and fatty acid substrate competition. Glucose and fatty acid substrate competition is commonly referred to as the "Randle cycle," so named to recognize the contribution that Randle and his colleagues made in postulating a mechanism by which FFA could induce insulin resistance The hypothesis is that oxidation of fatty acids by skeletal muscle, driven by a concentration-dependent uptake of plasma FFA, inhibits glucose oxidation and glycolysis, with consequent inhibition of the uptake of plasma glucose.

Because the mass of adipose tissue is increased in obesity and, more specifically, because suppression of lipolysis by insulin is impaired in obese individuals the metabolic milieu in obesity seems appropriate for glucose/FFA substrate competition to contribute to insulin resistance [23].

There is, however, skepticism regarding the relevance of substrate competition as a mechanism of insulin resistance in obesity. Higher ambient plasma FFA concentrations are often present in obesity hence operation of glucose/FFA substrate competition. The metabolic profile of insulin resistance in obesity with regard to glucose metabolism is a defect in glucose storage. This pattern does not seem to correspond to that predicted by Randle's hypothesis; hence glucose/FFA competition does not have a significant contribution to insulin resistance in obesity.

4. Mechanism of Diabetes

Insulin action is essential during this process. Under normal conditions, insulin blocks gluconeogenesis and glycogenolyis by inhibiting transcription of enzymes involved in these reactions (phophoenolpyruvate carboxylase, fructose 1,6-bisphosphate, and glucose 6-phoshatase) Simultaneously, in favors transcription of glycolytic enzymes, such as pyruvate kinase, and other lipogenic enzymes such as fatty acid synthase and acetyl-CoA carboxylase, thus promoting adequate homeostasis.

Regarding lipid metabolism, insulin directly inhibits lipolysis on adipose tissue around the liver thus preventing increase in levels of free fatty acid. Disruption of insulin signaling results in hyperglycemia, which in time, will translate into glucotoxicity, cellular deregulation, and progression to type 2 diabetes mellitus, and cardiovascular disease.

Hyperglycemia in patients with poorly controlled blood glucose levels increases de novo hepatic lipogenesis, favoring development of non-alcoholic fatty liver disease (NAFLD), hepatic insulin resistance, and progression to cirrhosis and severe liver disease such as hepato cellular carcinoma. Under an insulin resistant environment, increased activity of hepatic lipase and cholesterylester transfer protein (CETP) favor conversion of VLDL cholesterol into LDL cholesterol; and increased levels of VLDL increase catabolism of HDL cholesterol into atherogenic fat particles, thus triggering the physiopathological disorders.

Glucosidase, Pancreatic lipase plays a key role in the efficient digestion of triglycerides [25]. Lipases are involved in the hydrolysis of glycerides to glycerol and free fatty acids. The enzyme inhibition is one of the approaches used to treat obesity due to the fact that 50%-70% of total dietary fat hydrolysis was performed by pancreatic lipase FIG. 4 [26].

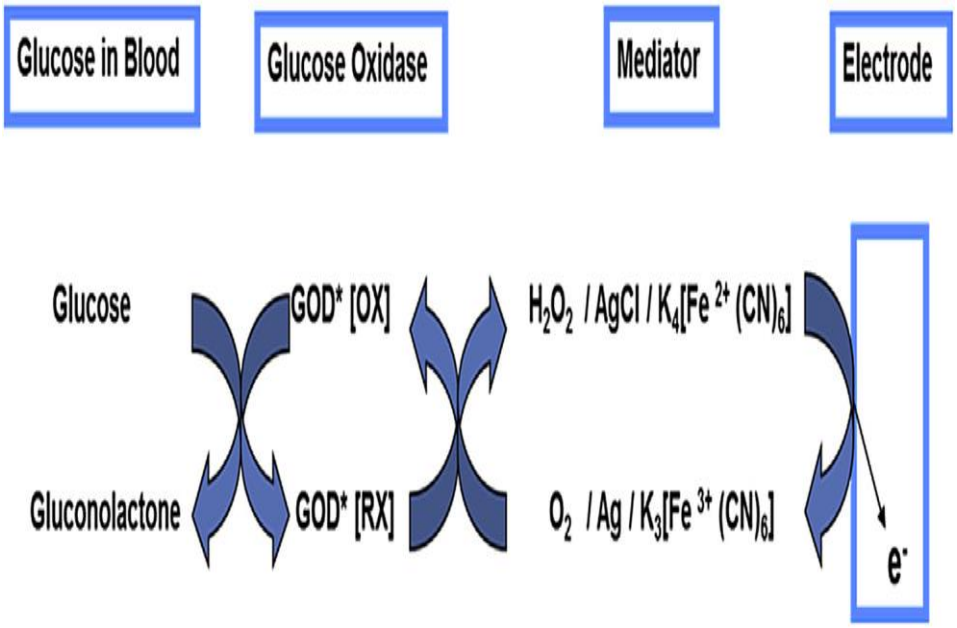


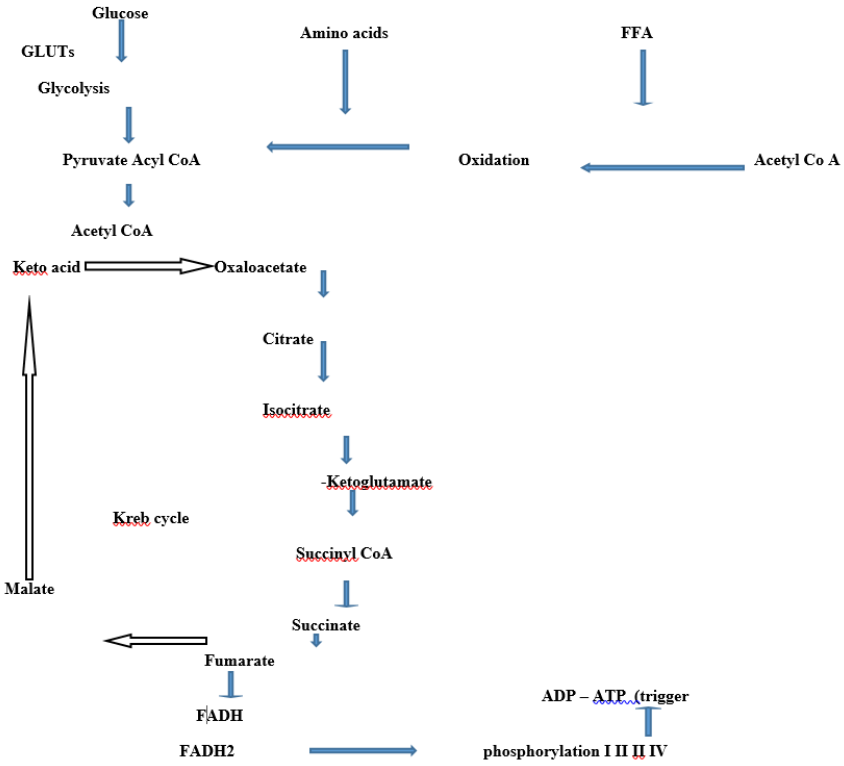
FIG. 4. **Enzyme-based electrode with glucose oxidase and mediators.**

The mechanism involves inhibition of dietary triglyceride absorption, as this is the main source of excess calories [26] besides, pancreatic lipase inhibition does not alter any central mechanism which makes it an ideal approach for obesity treatment [27]. This enzyme has been widely used for the determination of the potential efficacy of natural products and not as biosensor. But glucosidase have been used as seen in (FIG 4).

5. Glucose Production within The Mitochondria

Diabetes, a metabolic disease associated with impaired metabolism of proteins, fats and carbohydrates. However, most authors believe that diabetes is primarily a violation of carbohydrate metabolism (glucose). Glucose is the main source of energy, since the brain and blood cells use only glucose as an energy source, and only glucose can supply ATP energy under anaerobic conditions.

Glucokinase/hexokinase is an important enzyme involved in the transport of glucose into cells. The expression of this enzyme is controlled by the enzyme glucose-6-phosphate dehydrogenase (G6PDH), which forms part of the pentose phosphate pathway. Changes in this rate-limiting enzyme have been observed at sites of diabetes complications. Once glucose is transported inside the cell, most of it is metabolized via glycolysis, through steps involving the conversion of glucose-6-phosphate to fructose-6 phosphate. When intracellular glucose concentrations are however high from all over certain tissues and organs as shown in FIG. 5 below ATP dose trigger mutation of cell where they are pocketed.



FADH2, flavin adenine dinucleotide (reduced)

complex I (NADH dehydrogenase)

complex II(succinate dehydrogenase)

complex III (cytochrome *c* reductase) complex IV (cytochrome-*c* oxidase

FIG. 5. **Glucose production within the mitochondria.**

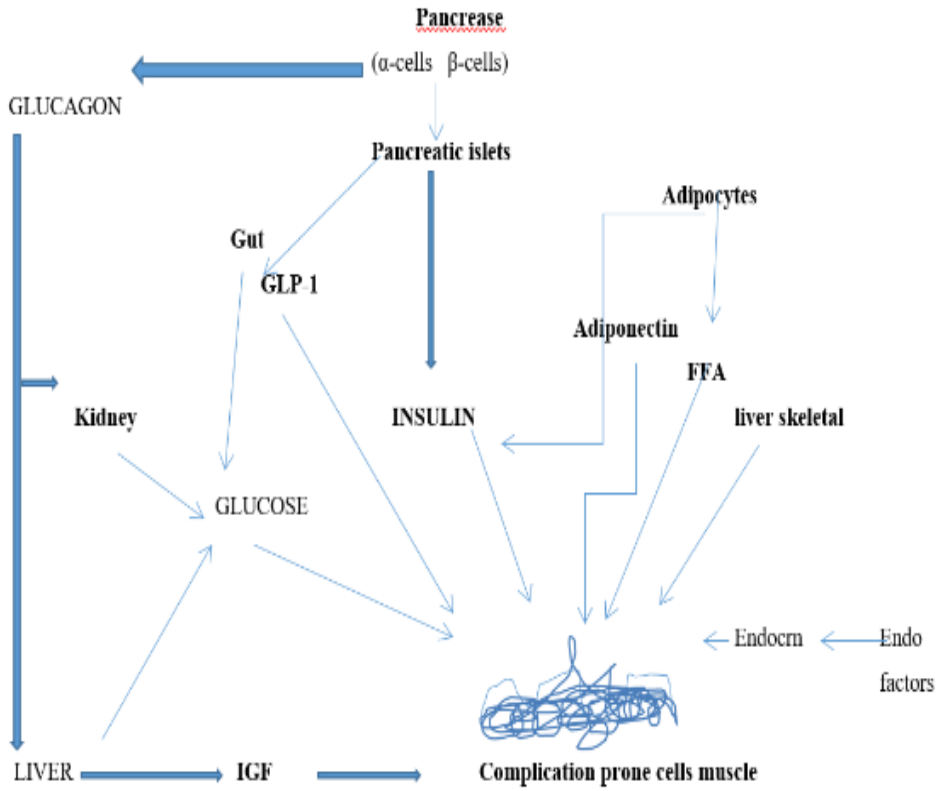
6. Glucose Homeostatic Pathways

All regulatory systems, all types of metabolism are involved in maintaining glucose homeostasis. There is convincing evidence that optimizing glycemic control by targeting a number of sites is the most effective therapeutic strategy in the clinical management of micro vascular complications of diabetes (FIG. 6). Studies have shown that more intensive glycemic control does not necessarily reduce the risk of cardiovascular disease.

Cells within tissues that are prone to diabetic complications, such as endothelial cells, are not able to modulate glucose transport rates to prevent excessive accumulation of intracellular glucose. Hence; energy production in these cells becomes uncontrolled in the context of diabetes and eventually is impaired. Glucose-derived molecules, which enter cells, are usually fed into the cells. There are numerous agents used to control hyperglycemia in type 2 diabetes. These include insulin-sensitizing agents such as thiazolidinediones and metformin, whose primary role is to improve insulin resistance and glucose uptake into peripheral tissues. Interventions that stimulate insulin secretion from the pancreas but with hepatic depression.

Some of these antihyperglycemic agents have direct effects on the development and progression of diabetic complications. For example, thiazolidinediones, which are peroxisome proliferator activated receptors (PPAR agonists), have shown beneficial

effects on complications, which are independent of their glucose lowering action. Indeed, the protective effects of PPAR agonists in the diabetic kidney appear to be modulated via prevention of activation of proximal tubular cells and reduced secretion of profibrotic cytokines such as hepatocyte growth factor and other factors (FIG. 6).



Target cells include endothelial cells, podocytes, proximal tubular cells, Muller cells, cardiomyocytes, and neuronal cells.
GLP-1, glucagon-like peptide;
IGF-1, insulin-like growth factor;
FFA, Free fatty acid

FIG. 6. **Glucose Homeostatic Pathways.**

7. Potential Mechanisms Linking Central Obesity to T2DM

Obesity is a heterogeneous condition with respect to regional distribution and biological properties of fat tissue [28]. Visceral adipose tissue refers to fat accumulation within mental and mesenteric fat depots, and constitutes about 6%-20% of total body fat tissue. It is less receptive to the anabolic effects of insulin and metabolically-lipolytically more active than the peripheral fat tissue, which refers to subcutaneous fat accumulation and comprises 80% of total adipose tissue.

The traditional views on metabolic derangements of diabetes have been largely ‘glucocentric’, considering hyperglycaemia the main underlying cause. However; the recognition that obese individuals who usually suffer from hyper- or dyslipidaemia develop insulin resistance and diabetes much more frequently than lean people and also that people with T2DM almost invariably manifest serious break down in lipid dynamics, reflected by elevated levels of circulating non-esterified fatty acids

(NEFAs) and triglycerides (TG), led researchers to investigate the potential role of altered lipid metabolism in the pathogenesis of T2DM.

Two theories mainly explain the close relationship between fat excess and impaired glucose metabolism; the 'Randle's cycle' that provides the reciprocal relationship between fatty acid oxidation and glucose oxidation and the 'ectopic fat storage hypothesis' according to which the impaired insulin effect is due to deposition of lipids within insulin-target tissues.

Recently, two more hypotheses were added to the suggested theories by which obesity may lead to T2DM; First, the identification of adipose tissue as an endocrine organ that produces and metabolizes multiple bioactive factors, which may potentially impair glucose metabolism and second, change of adipose tissue phenotype due to a low-grade inflammatory state that impairs insulin effectiveness. Although these theories provide metabolic mechanisms that seem to be different in origin and nature, the underlying trigger factor may be related to effect of substrate excess relative to what adipose tissue has the genetically determined capacity to store (Randle theory). As a result, obese individuals develop insulin resistance, which is initially compensated for by hyperinsulinaemia, through which normal glucose tolerance is preserved. However, over time further deterioration of glucose metabolism, either by increased insulin resistance or by decreased compensator.

8. Methods in Measuring Obesity.

8.1 Densitometry method [29]

8.2 Principle

Utilizes the principle of body density which is equal to mass over volume. It is used to estimate fat-free mass, fat mass and percentage body fat. The assumption is based on that density of fat =0.900 g/cm^3 and fat free mass =1.100g/cm^3 are relatively constant across individuals. However, growth, maturation, degree of illness of obesity and aging creates deviations.

8.3 Methods

Body mass in air and while immersed in water using Archimedes principle of apparent weight of an object immersed in water is relative to its weight in air. This is equal to the volume of water displaced. This method allows for visceral and lung corrections.

Prediction of body fat using body density measurements

Siri, 1956 $\%\ Body\ fat = \left(4.95 / D_b - 4.50\right) \times 100$

Brozek, 1963 $\%\ Body\ fat = \left(4.570 / D_b - 4.142\right) \times 100$

$$D_b = body\ density$$

9. Air-Displacement Plethysmography (ADP)

9.1 Principle

This measure body density through measurement of body mass and volume.

Air-displacement plethysmography is similar to hydrodensitometry in using mass and volume to measure body density.

9.2 Method

These methods use the displacement of air to estimate body volume. (Life Measurement). Body composition analyzer contains two-compartment chamber of known sizes (FIG. 7).

FIG. 7. **Pod pea pod.**

A pulsating diaphragm between the two chambers vary the pressure, by displacing the air when a subject is seated in the outer chamber and is measured. A breathing apparatus is built into the device to estimate lung volume for a more accurate estimate of body density. Body density is determined; the calculations are similar to those for hydro densitometry. The Pea Pod is designed for infants, who are placed in the chamber without clothing or diapers. The measurement time is approximately 3-5 min.

10. Dixon Method

10.1 Principle

Exploiting chemical shift differences between water and fat magnetic resonance signals via echoes. The Dixon approach generally collects anatomical images with water and fat signals encoded differently in two or three imaging acquisitions.

10.2 Method

Dixon method selects several gradient echo times to allow the evolution of magnetic resonance signals according to their chemical shifts. Water and fat-only images are calculated from these resulting Dixon images (TABLE 1 and 2).

TABLE 1. **Summary on in-vitro Test for Obesity.**

***In-vitro* test**	**Principles**	**Uses**	**Reference**
plurality of polymorphic genes	Genetic mapping	Not common and expensive	[37]
Dual-energy X-ray absorptiometry (DXA)	photon emission and attenuation of the x- ray beams	Not common and expensive	[26]

Metreleptin immune response	Leptin immune response	Not common and expensive	[30]

TABLE 2. **Summary table on *in-vivo* Test for Obesity.**

In-Vivo	**Principle**	**Uses**	**Reference**
Computational Temography scan	X-ray attenuation	Not Common/ expensive	[9]
Air displacement plethysmography	Density	Not common	
Dixon method	Water and fat magnetic resonance signals via echo	Common but expensive	
Densitometric method	Archimedes principle	Common	[32]
MRI	Hydrogen atom excitation via magnetic field application	Not Common and expensive	
BMI	Weight –height ration	Common and less expensive	[5]
Waist /Hip ration/wait –hip circumferences	ration	Common and less expensive	[5]

11. Methods of Measuring Diabetes-*In-Vitro* Model Analysis

11.1 Pancreatic α-amylase methods

11.2 Principle

Pancreatic α-amylase, an important enzyme of digestive system hydrolyzes starch into mixture of smaller oligosaccharides comprising of maltose, maltotriose and oligoglucans which are further degraded by glucosidase into glucose that enters the blood stream upon absorption.

11.3 Methods

The assay mixture of test sample, PPA, starch solution prepared using 500 µL of 0.02 M sodium phosphate as a buffer (pH 6.9) and incubated at 37^{o}C for 10 min.

Add starch buffer and incubated at 37°C for 15 min again.

Add Dinitrosalysilic acid (DNSA) reagent (1.0 mL) to halt rxn.

Placed in boiling water bath for 5 min, cooled, diluted and measured at 540 nm.

The control without test sample and the absorbance produced by test sample measured

$$Percentage\ assay = \frac{Abs\ of\ \ control - Abs\ of\ \ sample}{Abs\ of\ \ control} \times 100$$

12. α-Glucosidase Methods

12.1 Princple

α-Glucosidase and Sucrase are confined to the mucosal brush border of the small intestine and catalyze the final step of digestion of starch and sucrose. The lowering of postprandial blood glucose and insulin levels in diabetic patients is due to the delayed breakdown of carbohydrates in small intestine by the α-glucosidase and sucrase inhibitors [31-35].

12.2 Methods

Assay mixture of α-glucosidase enzyme solution with test samples of different concentration, phosphate buffering to pH 8 and incubate at 37°C for 10 min in maltose solution.

The quantity of glucose liberated is measured for 2 min in boiling water

Test sample with Enzyme solution (ET) for 10 min at 37°C incubation for enzyme activity test.

The standard control without test sample represents 100% enzyme activity (EC).

The α- glucosidase inhibitor (acarbose) can be used as a positive test control (TC).

The % of inhibition for α-glucosidase is calculated at 540 nm

$$\%\ Inhibition = EC - \left(ET - TC\right) / EC \times 100$$

Where, EC is enzyme activity of control, ET is enzyme activity of test and TC is test control

13. α-amylase Inhibition Assay

13.1 Principle. inhibition assay

13.2 Methods

Add test sample with α- amylase enzyme and Incubated

Add starch solution and incubation for 2h at 30°C (control)

Add dinitrosalicylic acid reagent to both control and test to halt reaction

Keep this mixture in boiling water bath for few minutes.

The absorbance was taken at 540 nm using spectrophotometer.

$$\%\alpha - amylase\ inhibition = \frac{Abs\ of\ \ control - Abs\ of\ \ sample}{Abs\ of\ \ control} \times 100$$

14. α-Sucrase Method

14.1 Princple: Inhibition of glucosidase assay

The enzyme and sample incubation for 10 min at 37°C. Buffering at (pH 6.0) using malate and up volume to 200 µL/?. sucrase solution (60 mM) and incubating mixture for 30 min initiates reactions.

Add 200 µL 3,5- dinitrosalysilic acid (DNS) with the mixture in a boiling water bath for 5 min halt the reactions.

The absorbance of the solution is read at 540 nm.

$$Sucrase\ inhibition\ rate\ is\ calculated\ thus = \frac{Abs\ of\ \ control - Abs\ of\ \ sample}{Abs\ of\ \ control} \times 100$$

Where, AC control is the absorbance of the control reaction (all reagents to be added except for the test sample), and the AS sample is the absorbance of the test sample. Models to target Specific/Particular enzyme.

15. *In-Vivo* Methods of Diabetes Analysis

15.1 Hemoglobin glycosylation Test

15.2 Principles hypotonic and centrifugal principle

15.3 Methods

Blood from subject is first separated by column chromatography.

Collected blood is placed in a bottle and then mixed with NaCl and hemolysate made according, based on hypotonic principle**.**

Hemolysate is centrifuge at 15 rpm. Hemoglobin rich fractions are collected and then added to different fractions.

Fraction of glucose and other text solution (control) prepared in buffer solution.

The reaction mixture is kept for 72 hrs at 25°C incubated.

Glycated hemoglobin is spectrophometrically determined at 540 nm.

$$\%\ Inhibition = \frac{Abs\ of\ \ control - Abs\ of\ \ sample}{Abs\ of\ \ control} \times 100$$

15.4 Glycosylated serum proteins test

The degree of glycation of serum proteins (mostly albumin and fructosamine) provides an index of glycemic status over certain 1-2 week (the half-life of albumin is 14-20 d). This test is useful especially in a situation in which HbAlc assay is subject to interference

15.5 Fasting plasma glucose (FPG)

FPG requires an overnight fast of at least 8 hrs. The results of FPG are more reproducible over a short term than those of OGTT.

15.6 Oral glucose tolerance test (OGTT)

In compliance with the most recent American Diabetes Association (ADA) recommendations, OGTT is not indicated for routine use with the exception of pregnancy.

15.7 Intravenous glucose tolerance test (IVGTT)

The intravenous glucose tolerance test (IVGTT) is an important dynamic test used to evaluate residual β-cell function in patients with type 1 diabetes mellitus. It is also useful in the screening of siblings of patients with type 1 diabetes or in the evaluation of glucose tolerance in patients with malabsorbtion.

Fasting plasma glucose (measured before the OGTT begins) is below 6.1 mmol/L (110 mg/dL). Fasting levels between 6.1 and 7.0 mmol/L (110 and 125 mg/dL) are borderline ("impaired fasting glycaemia"), and fasting levels repeatedly at or above 7.0 mmol/L (>126 mg/dL) are diagnostic of diabetes.

15.8 Monosodium glutamate induced diabetes

Monosodium glutamate (MSG) cause increase in plasma glutamate concentration. MSG stimulates insulin release. Administration of MSG in mice resulted in obesity associated with hyperinsulinemia. After 29 weeks, level of blood glucose, total cholesterol and triglyceride levels were increased [36].

15.9 Insulin antibodies induced diabetes Karthikeyan

The insulin antibodies have the affinity and capacity to bind insulin. Insulin deficiency mechanism may cause greater postprandial hyperglycemia because antibody-bound insulin is unavailable to tissues, but the prolongation of postprandial hyperinsulinemia may lead to hyperglycemia [36].

16. Spontaneous Diabetic Non Obese Rodent Models Karthikeyan

16.1 Goto Kakizaki (GK) rat

The GK rat is a non-obese model of T2DM with hyperglycemia, hyperinsulinemia, and insulin resistance. In GK rats a stable fasting hyperglycemia was observed at the end of the first 2 weeks. After 8 weeks, hyperglycemia degenerates and insulin secretion of the islets stimulated by glucose. GK rats, develops complications of diabetes like peripheral neuropathy, and retinopathy [36].

16.2 Cohen diabetic rat

Cohen diabetic rat is a genetic model derived from diet-induced Type 2 DM model by placing the rat on a synthetic 72% sucrose-copper-poor diet for 2 months, manifest the human Type 2 DM. The manifestations include non-obesity, hyperinsulinemia, and insulin resistance. The Cohen diabetic rat expresses genetic susceptibility to a carbohydrate-rich diet, a feature of Type 2 DM in human [37].

16.3 Spontaneously Diabetic Torii (SDT) rat

SDT rat is a new spontaneously non-obese diabetic strain. It has characteristics like glucose intolerance, hyperglycemia, hyperinsulinemia, and hypertriglyceridemia. Because of the severe hyperglycemia, SDT rats develop diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy. This model is suitable for studying complications of human T2DM (FIG. 8) TABLE 3 and 4 [36].

TABLE 3. **Summary on *in-vitro* test for diabetes.**

***In-vitro* test**	**Principle**	**Uses**	**Reference**
Pancreatic α amaylase	Enzyme hydrolysis of starch (Pancreatic amaylase)	Common / not cheap	[1]
α- glucosidase	Enzyme hydrolysis of starch(α- glucosidase inhibition)	Common / not cheap	[1]
Sucrase method	Inhibition of glucosidase	Common / not cheap	[1]

α-Amylase inhibition method	α-Amylase inhibition	Common / not cheap	[1]
Aldose reductase activity method	Aldose reductase assay	Not Common / not cheap	[33]
Pancreatic cholesterol esterase method	Pancreatic esterase inhibition assay	Not Common / not cheap	[33]

TABLE 4. **Summary on *in-vivo* test for diabetes.**

In-Vivo	**Principle**	**Uses**	**Reference**
Monosoduim glutamate test	Inhibition of glucosidase	Common /not cheap	[31]
Sponteneous non obese rats	Inhibition of glucosidase	Common /not cheap	[31]
Sponteneous Diabetes torii rats	Inhibition of glucosidase	Common /not cheap	[31]
Blood glucose test	Absorptive affinity	Common/ cheap	
Insuline anti- bodies	Insuline anti body affinity	Common /not cheap	[31]
Cohen diabetic rat	Inhibition of glucosidase	Common /not cheap	[32]

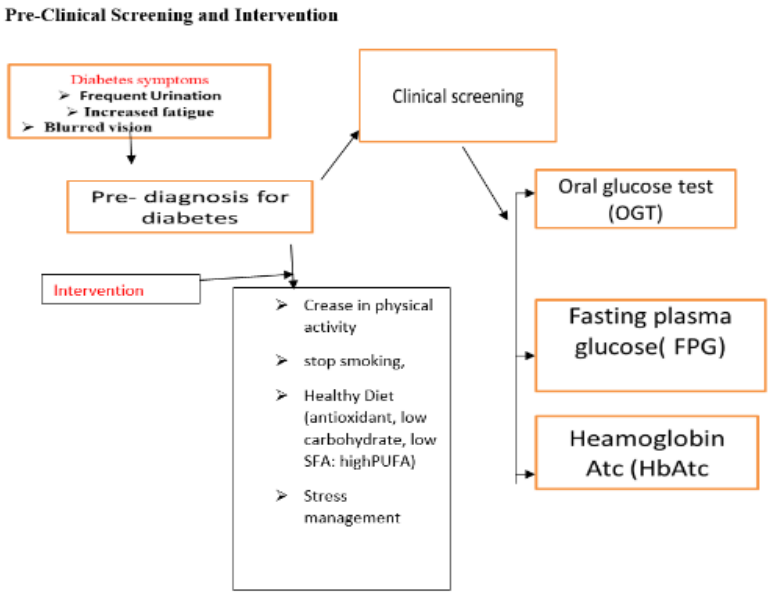


FIG. 8. **Pre-Clinical Screening and Intervention.**

17. Conclusion

Diabesity, a pathophysiological link between obesity and diabetes is becoming pandemic. Obesity is attributed to fatty deposits and their differential in visceral and other tissues, conferring anthropometry approaches for their determination. The lipase activities, triglyceride absorption and glucose fatty acid uptakes as well as glucosidase inhibitive mechanisms are the major cause of sugar increase, underlined diabetes nutritional disease in human. This causative had attracted the *in-vitro glycosidase*, sucrose and amylase methods of diabetes measures and *in-vivo* hemoglobin glycalation and animal models tests. Advocacy on molecular nutrition and functional food formulation and use could help aliomerates the pending epidemics and or future pandemics of obesity and diabetes in developed and developing countries. The dietary measures offer the most viable and effective solution to diabetes onset in addition to the obese state rather than pharmaceutical drugs. The designing of a smart diet (i.e. healthy diet) and selecting gut microbiota having probiotic influence on the host can trigger weight reduction/ management, in addition to stabilizing sugar levels in the blood of an individual. Additionally, the regular physical workout can help an individual in controlling body weight and regulate other biochemical conditions which does lead to various types of metabolic disorders.

18. Recommendations

Studies on Urbanization, light intensity in relation to dieting and life styles should be researched and projections made in developing countries with specific diet formulation across all age groups in the society.

Bio-camera for diabetes and obesity determination should be developed to easily screen and ascertain patient for clinical and pre-clinical counseling because obesity and diabetes are mediated.

Scientists in food and health areas should bear in mind and get ready to make food bioactive and functional foods from local food sources or blends that would impinge obesity and diabetes diseases build up such like pharma foods.

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