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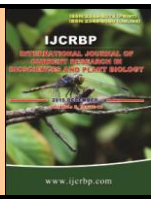

Review Article

Role of Adipocytes and Fatty Acids in Metabolic Pathways of Glucose Intolerance Leading to Diabetes Type-2

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Abstract

Most of the body functions are performed by maintaining energy homeostasis especially by control of blood glucose level. Almost 65% of population worldwide dies due to obesity. Almost 80% of patients having T2DM from United States are bulky, and both are thin, particularly obese type 2 diabetics not considered by day-long advancements in fatty acid (FFA) which is plasma free concentration, that usually subdues after ingestion of one food or mixed oral glucose capacity or in reaction to the insulin. . *In vitro* studies have verified that plasma FFA are effective stimulators of HGP and motivate pyruvate carboxylase and phosphoenolpyruvate carboxykinase, the rate-limiting enzymes for gluconeogenesis. The view that the compartment of adipocyte is a significant factor of the standard and deviant energy equilibrium and its related disorders originates from the connotation that has been shown among obesity and the metabolic syndromes.

Keywords

AMPK pathway

Free fatty acids

Impaired glucose tolerance

Insulin

Type 2 diabetes

Introduction

One of the fundamental tasks of the body which has to be performed is maintaining energy homeostasis, and it is mainly achieved by the control of blood glucose level. Therefore, normoglycemia is controlled through accurate energy delivery to the energy-requiring tissues or the storage in adipose tissue by the compartment of lipoprotein (Patti et al., 1995). The processes comprise multitudes of highly tuned and tightly regulated mechanisms that is only partially involved and understood in all tissues. Nonetheless, the adipose tissue and specifically adipocytes along with the liver and skeletal muscle appear to be the most important organs for dealing with challenges to maintain the body energy and to maintain the energy's metabolic system in homeostasis. Though, throughout most of the mankind's history the lack of energy has been the foremost challenge in existing societies because the excess consumption of calories, particularly fats and sugars along with their main manifestation and diseases related to hyperglycemia has become a serious problem. The condition is elevated by the upsurge of sedentary life-styles and specially the use of great levels of tobacco (Patti et al., 1995; Shirmomura et al., 2000). Presently, 65% of the worldwide population lives in such countries where obesity kills more individuals than malnutrition (WHO - Global policy on diet, physical movement and health, 2010). The metabolic syndromes include lipo-dystrophy, obesity-induced metabolic syndrome and

Type 2 Diabetes Mellitus (T2DM), which signify an ever growing challenge to health-care (Gavrilova et al., 2000).

The metabolic system of energy controls the energy use in body and it is difficult to classify. It mainly constitutes energy storing and transporting molecules, lipoproteins (lipid carriers), the metabolically active tissues (like adipose tissue, liver, skeletal muscles and kidney), the endocrine system (e.g. pancreas, hypothalamus, adipose tissue, thyroid, growth hormones and adrenal gland hormones) and also the metabolic pathways (mostly Adenosine Monophosphate-Activated Protein Kinase (AMPK), insulin and all inflammatory molecules (Unger et al., 2001). Significant evidence also associates altered fat topography and the deranged adipocyte metabolism in the pathogenesis of glucose intolerance cases in T2DM 1) the Fat cells are resilient to insulin's anti-lipolytic influence, causing raised plasma FFA levels for day long. Gluconeogenesis is stimulated by persistently increased plasma FFA, inducing muscle or hepatic insulin resistance, and it also impairs insulin excretion in genetically predisposed persons. Such FFA-persuaded disturbances are called lipotoxicity; 2) The excessive quantities of insulin resistance-induction, seditious, and Atherosclerotic-inciting cytokines are produced by dysfunctional fat cells and it fails to secrete the normal quantity of insulin-alerting adipo-cytokines; 3) Inflated fat cells have diminished capacity to store fat and are insulin resistant. When the storage capacity of adipocyte is exceeded, the lipid "overflows" in liver, muscle and possibly cells, resulting in decreased insulin secretion and muscle/ hepatic insulin resistance. Thia-zolidinediones improve adipocyte insulin sensitivity (Nagaev, 2001).

Approximation of the sensitivity of whole-body insulin and the action with the euglycemic lock technique is basically an image of the glucose removal by the muscles which is 60 – 70%. The adipose tissue merely constitutes 10% of the insulin-stimulated complete body glucose endorsement and the liver accounts for 30% only (Maeda et al., 2001). Therefore, lessened insulin-stimulated glucose disposal in a euglycemic clamp is mostly due to a condensed glucose endorsement by the muscles of the body. This statement has headed to the conclusion that whole body insulin resistance not only happens in, but also initiates in the muscles. This result is evidently not consistent with an insignificant role of the adipose tissue intended for the disposal of whole-body glucose (Frayn et al., 2003).

Types 2 diabetes

The influence of insulin, one or the other like added in vitro or infused in vivo, on transport of glucose and signaling of insulin in skeletal muscles as of type 2 diabetic issues has been reviewed recently. The major outcome is that a damaged insulin-stimulated tyrosine phosphorylation of IRS-1 is related with reduction of 50% in PI3-kinase movement. (Margetic et al., 2002) However, the downstream initiation of the significant serine=threonine kinase PKB=Akt seems to be regular or simply damaged in the existence of a supra-physiological insulin deliberation by in vitro addition. The damaged tyrosine phosphorylation does not seem to be owed to a reduced IRS-1 protein appearance, though lesser levels have been comprehended in few cells in gestational diabetes. An amplified serine phosphorylation of IRS-1 may lessen the insulin-stimulated tyrosine phosphorylation, nonetheless it is presently unknown whether this is the case in type 2 diabetes or not. Altogether, the data advocates that the activation of PI3- kinase, and apparently the production of PI3, 4- and PI3, 4 and5 phosphates, are reduced but still adequate to let a usual initiation of the downstream signing actions. This has headed to the inference that resistance of insulin in skeletal muscle is triggered by the damaged stimulation of effector or motioning molecules downstream of PKB=Akt.

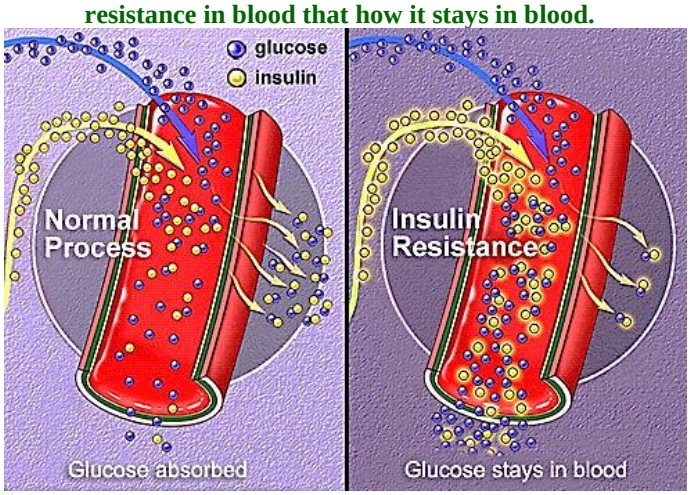
Glucose transport of Insulin-stimulation is also concentrated in skeletal muscles as compared to type 2 diabetic issues. Unexpectedly, though, recent in vitro researches have revealed that this seems to be largely caused by 'glucose toxicity'. The effect of insulin is impaired by pre-incubating the tissue biopsies for only 2h at increased glucose concentration. Whereas, the insulin response is normalized by pre-incubating diabetic muscle shreds for 2h at a biological glucose concentration. Though, it is also probable that the pre-incubation period incapacitates the consequence of further circulating contenders to insulin acts such as TNFα, free fatty acids (FFA) and the interleukins. Altogether, presently available facts suggest that there are only diffident and apparently not functionally damages or interruptions in insulin signing upstream of PKB=Akt in skeletal muscle since type 2 diabetic issues. Moreover, the damaged insulin-stimulated glucose transference appears to be quickly reversible in-vitro through pre-incubating the tissue trials in fresh medium comprising of a biological glucose concentration. These conclusions are similarly in consent with the reliable

demonstration that the GLUT4 protein material and expression of mRNA are usual in skeletal muscle in the type 2 diabetes.

The condition is somewhat dissimilar in the adipose tissue. There is a marked reduction in the insulin-stimulated tyrosine phosphorylation of IRS-1 of the adipocytes from type 2 diabetic issues. Though, it is basically due to a 70% decrease in IRS-1 protein appearance. Likewise, total PI3-kinase working is condensed to 70%. In comparison, IRS-2 expression is usual and then this molecule turns out to be the chief docking protein for insulin-stimulated PI3-kinase activation. Thus the downstream activation of PKB=Akt is also markedly impaired with the reduced PI3-kinase activation, mostly due to main decline in the insulin-stimulated serine phosphorylation (Withers et al., 1999).

The transport of glucose in reaction to the insulin is reduced from type 2 diabetic subjects in fat cells because of both the marked reduction (70 – 80%) and impaired insulin signaling in mRNA expression and GLUT4 protein. In the muscle cells comparison as discussed above, at physiological (5.6mmol=l) level, the pre-incubating human fat cells for 16h or the increased glucose concentrations (16.8 and 25mmol=l) cannot damage the severe stimulatory effects of insulin on glucose (Kubota et al., 2000) endorsement neither does the pre-incubation of physical glucose concentration of diabetic cells restore the severe insulin response after 6h (these are not published observations). This is steady with the condensed GLUT4 protein manifestation in adipocytes that perhaps needs an extended time for the setback (Considine and Caro, 1997).

Fig. 1: Illustration of normal process and insulin resistance in blood that how it stays in blood.



Insulin secretion

Beforehand the inception of the post-prandial and hyperglycemia of fasting, entities genetically pre-disposed to form T2DM are called resilient to the action of the insulin. However, homeostasis of glucose stays usual because of an obvious rise in insulin exudation by the pancreatic cells (Zhang et al., 1994). The escalation of the fasting insulin concentration of plasma is adequate for compensation of the resistance of hepatic insulin, and then the basal level of hepatic glucose production (HGP) stays usual, while the hyper-insulinemic reaction to ingestion of carbohydrate is adequate to cause usual clampdown of the basal HGP and to suppress the flaw in muscle glucose endorsement. Along with the beginning of impaired glucose tolerance (IGT), the deterioration of the insulin resistance in muscle and liver takes place and the upsurge in the total insulin reaction to an uttered glucose contents (Campfield et al., 1995). Though, disruption in the scheduling of insulin discharge in IGT, with deterioration in primary stage insulin excretion, is followed by an undue late stage insulin reactions (Pelleymounter et al., 1995). The development from IGT to manifest T2DM is linked with minute or no more decline in insulin resistances (Campfield et al., 1995). Somewhat, there is decrease in the aptitude of the pancreas to sustain its elevated insulin secretory level (Halaas et al., 1995)), causing deterioration of intolerance of glucose and then ultimate improvement of manifested T2DM. The reversed U-shaped bend of insulin secretion, like individuals' grow from usual tolerance of glucose to IGT to T2DM is called Starling's arc of the pancreas (Campfield et al., 1995). Primarily, the flaw in homeostasis of glucose is obvious by an undue increase in the excursion of post-prandial glucose (in IGT and mild diabetes), then this is tailed by increase in the plasma glucose concentration of fasting level.

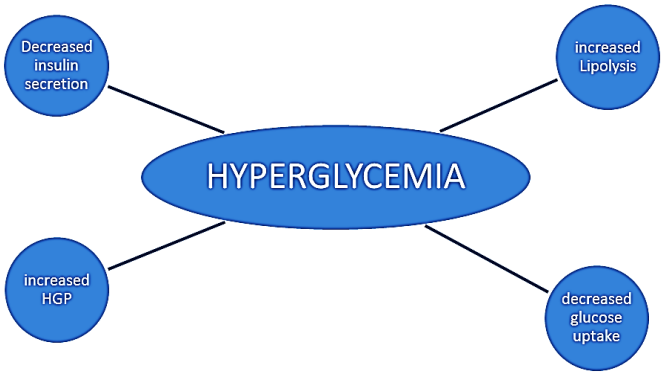
Role of adipocyte and FFA in T2DM pathogenesis: The dysharmonous quartet

Almost 80% of patients having T2DM from United States are weighty (Tartaglia et al., 1995), and both are thin, particularly obese type 2 diabetics not considered by day-long advancements in fatty acid (FFA) which is plasma free concentration, that usually subdues after ingestion of one food or mixed oral glucose capacity or in reaction to the insulin. Alike abnormalities in metabolism of FFA have accepted in personalities with non-diabetic, IGT and insulin-resilient obese persons (Campfield et al., 1995). FFA is deposited as

triglycerides in fat cells and function as a source of energy during conditions of fasting. Insulin is in effect the inhibitor of lipolysis (Tartaglia et al., 1995) and it hinders the discharge of FFA from the adipocytes by constraining the lipase enzyme which is sensitive to hormone. In patients of type 2 diabetes, the capability of insulin to prevent lipolysis then lessens the plasma concentration of FFA considerably pretentious (Tartaglia et al., 1995). It is now familiar that the persistently increased concentrations of plasma FFA create resistance to insulin in liver and muscle (Levin et al., 1996) and the secretion of insulin (Tartaglia et al., 1995) do not affect. Hence, amplified levels of plasma FFA intensify the three basic disorders of pathogens which are accountable for homeostasis of impaired glucose in individuals having T2DM, and the phase has achieved for the "triumvirate" (muscle, liver and cells) are connected by the "fourth musketeer "(Singh et al., 2009a) to the "disharmonious quartet" system (Fig. 2).

Addition of FFA to flow in plasma in elevated quantities, patients with T2DM have stocks in the triglycerides in the muscle is amplified (Nakashima et al., 1997)), in addiction the liver (Tartaglia, 1997) that strictly relate with the existence of resistance of insulin in such tissues. In the liver and muscles the triglycerides is a condition of stagnant revenue and metabolites of intracellular lipolysis of tryglyceride impair insulin action in both muscle and liver (Tartaglia, 1997). This arrangement of occasions is like lipotoxicity (Singh et al., 2009b) correspondingly. It has gathered evidence to involve lipotoxicity also like any significant reason of dysfunction of cell (Nakashima et al., 1997).

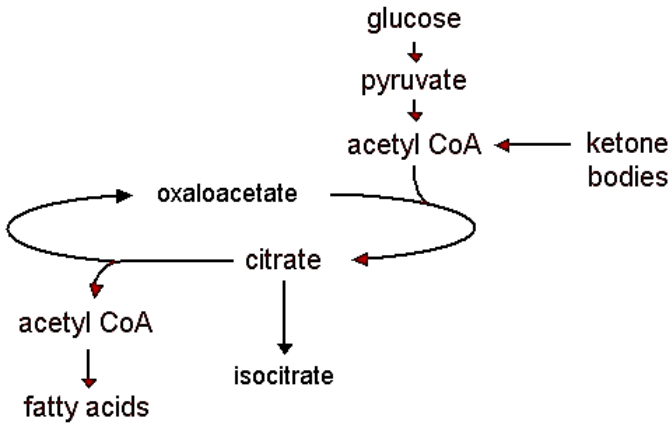
Fig. 2: The dysharmonious quartet.



FFA and hepatic glucose metabolism

The liver shows a vital role in the guideline of metabolism of glucose (Singh et al., 2009a). After the absorption of a meal of carbohydrate, then the mixture of hyper-insulinemia and hyper-glycemia suppress the production of basal hepatic glucose (Jansen et al., 2009). Marked hyperglycemia would ensue if glucose were to go in the systemic circulation instantaneously from both the stomach and the liver. Furthermore, the liver takes up about one third of the glucose in the consumed carbohydrate meal (Singh et al., 2009a). Together, destruction of production of hepatic glucose and extension of hepatic glucose endorsement account for the conservation of about half of the increase in concentration of plasma glucose after ingestion of carbohydrate (Singh et al., 2009a). The regulation of HGP is measured by numerous features of which most important are insulin (constrains HGP) and glucagon and FFA (motivate HGP). *In vitro* studies have verified that plasma FFA are effective stimulators of HGP and thus by motivating pyruvate carboxylase and phosphoenolpyruvate carboxykinase, the rate-limiting enzymes for gluconeogenesis (Jansen et al., 2009), and by aggregating the movement of glucose-6-phosphatase, the enzyme that eventually controls the discharge of glucose by the liver (Guilherme et al., 2008).

Fig. 3: The glucose-fatty acid cycle relationship between FFA and metabolism and glucose.



Normally, the proliferation in concentration of plasma FFA excites gluconeogenesis (Jansen et al., 2009), while a decline in the concentration of plasma FFA decreases gluconeogenesis (Guilherme et al., 2008). Bergman, Cherrington and colleagues (Mitchel and Moyle, 1997) have revealed that an important constituent of thesuppressive influence of insulin on HGP is interceded via inhibition of lipolysis and decline in the concentration of plasma FFA. Furthermore, decline of the concentration of plasma FFA with nicotinic acid decreases HGP and gluconeogenesis in T2DM issues. In the resistance of insulin, standard glucose-tolerant

progeny of two diabetic parentages, suppression of HGP by insulin is condensed and is basal, and insulin-suppressed amounts of lipid oxidation and plasma FFA are impaired (Wang and Nakayama, 2010). Further insulin-resistant conditions, together with obesity and IGT, insulin-suppressed HGP is also reduced and associates with both the raised levels of basal FFA and the amplified rate of lipid oxidation (Cole, 2009). According to recent study (Mitchel and Moyle, 1967), normal glucose tolerance, insulin-resistant men verified damaged conquest of HGP and plasma FFA levels by insulin and amplified hepatic fat material, with strong associations among the three self-determining variables.

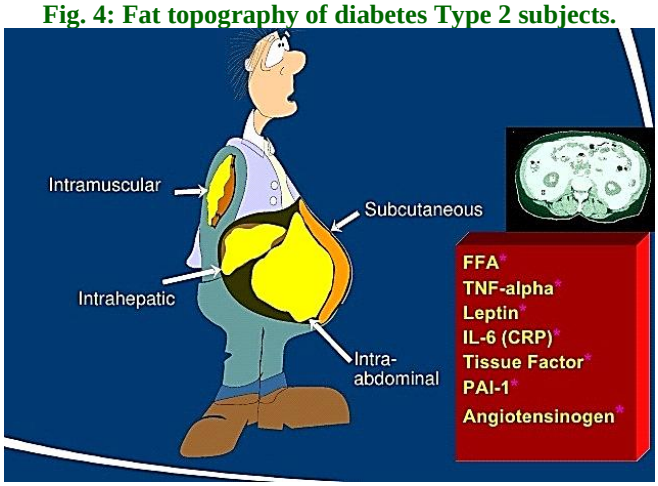
The affiliation between raised concentration of plasma FFA, FFA oxidation, and HGP in T2DM (and obesity) can be described as: 1) Amplified plasma FFA by mass deed enlarges FFA endorsement by hepatocytes, causing accelerated lipid oxidation and amassing of acetyl CoA. Amplified acetyl CoA motivates pyruvate carboxylase and phosphoenol-pyruvate carboxykinase, the rate-limiting enzymes in gluconeogenesis (Cole, 2009), along with glucose-6-phosphatase, the rate-controlling enzyme for glucose is released from the hepatocyte (Wellen and Hotamisligil, 2005). 2) Augmented FFA oxidation offers basis of energy (like ATP) and condensed nucleotides (NADH) to regulate gluconeogenesis. 3) Raised plasma FFA persuades resistance to hepatic insulin by hindering system of the insulin signal transduction (Hotamisligil et al., 2008). In patients of T2DM, these toxic effects of raised concentration of plasma FFA occur in recital with augmented plasma glucagon levels, amplified hepatic sensitivity to glucagon (McMahon et al., 2011), and augmented hepatic endorsement of mingling gluconeogenic precursors (Hattori et al., 2004).

Fat topography: Ectopic fat, insulin resistance, and β-cell failure

The link between obesity and T2DM is recognized well. Studies of prospective (McMahon et al., 2011) have shown that the occurrence of diabetes increases sharply with growing weight of the body. The diabetogenic result of obesity is associated with three factors: body mass index (BMI), obesity, time and current upsurge in weight of the body as shown in Fig. (Hattori et al., 2004). Epidemiologic facts (Meijer et al., 2011; Dennison et al., 2007) along with the direct amount with the clamp of euglycemic insulin procedure (Hattori et al., 2004; Nishino et al., 2008) have recognized obesity in a state like in insulin-resistance, and for the development of T2DM, both obesity and insulin resistance are taken as risk causes (Hattori et al., 2004; Cinti, 2002). Resembling to T2DM, the resistance of insulin to obesity includes liver, muscles, and the adipocytes (Nishino et al., 2008). Moreover, the total fat material and the design of fat circulation is also a significant predictor of the physique's sensitivity to insulin. Persons with privileged upper body fat accretion (android) are more resistant to insulin, hyper-insulinemic, and dyslipidemia as compared to the people with a pre-ponderance of lower Fig. fat (called gynecoid) (Rousset et al., 2004; Saely et al., 2012).

By means of magnetic resonance imaging (MRI) and computed tomography, the amplified visceral fat has been exposed to be precisely related to the incidence of resistance to insulin (Rousset et al., 2004). This link has been endorsed to the improved lipolytic action of visceral fat cells, with amplified delivery of FFA in the entry (producing resistance to hepatic insulin) and systemic (producing resistance to muscle insulin) transmissions (Saely et al., 2012). Nonetheless, there is also evidence to specify that visceral fat cells yield excessive quantities of adipocytokines (i.e. resistin, TNF, IL-6, PAI-1, etc.) which are insulin-resistant, and under secrete insulin-sensitizing adipocytokines (i.e. adiponectin) and inflammatory-provoking (Susulic et al., 1995; Xiang et al., 2011).

Fig. 4: Fat topography of diabetes Type 2 subjects.



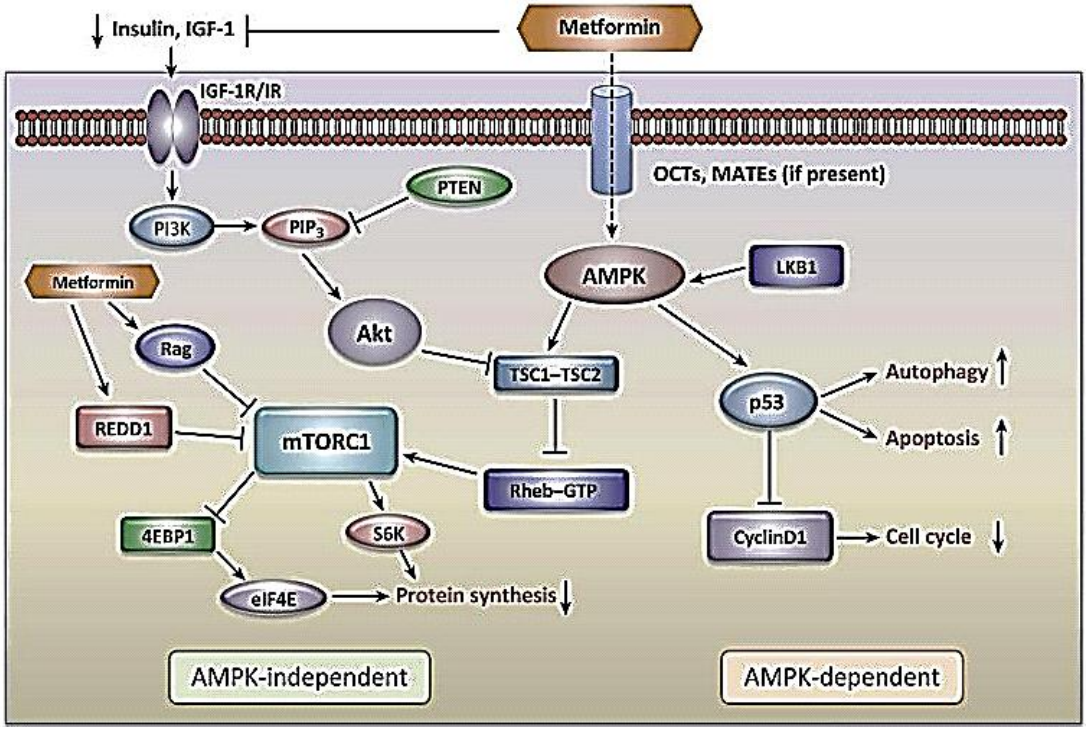
The link between obesity and diabetes

The view that the compartment of adipocyte is a significant factor of the standard and deviant energy equilibrium and its related disorders originate from the connotation that has been shown among obesity and the metabolic syndromes. Obesity is the new main jeopardy

globally. An excess of the energy in shape of triglycerides inside lipid precipitations of adipocytes is the foremost reason of obesity (Susulic et al., 1995). Many epidemiological surveys associate the hypertrophy of compartment of adipocyte to the energy metabolic syndromes like type 2 diabetes mellitus and insulin resistance and their infirmities including atherosclerosis, coagulopathy and cardiovascular disorders. The intensity of the problem is then compounded by the thought that together the obesity and its related disorders appear to show even more incidence in the world. The features motivating the epidemic of obesity are basically both the variations in diet with a more reliance on sugars and fats with an associated reduction in fiber in mixture with decreased physical movement. Likewise, it stayed an issue due to the failure to cultivate a therapy when talking about metabolic disorders. The improvement of humanity has certainly involved many episodes of risky starvation and consequently we are vastly talented of storing excess amount of energy in the body in the form of lipids for later utilization. The physiological place for the storage are the subcutaneous fat layers and it also protects us against cold (Ronnet et al., 2008).

Throughout the action, the deposited energy is released permitting better endurance. Though, worldwide calorie limit is not much of an issue now, obesity is disappointingly very public. Effective breakdown of fat can be then coupled by dissimilarities among persons in comparison to the threshold intensities of lipid release and storage as well as in the variance in the gut flora constituents. In order, obesity aggravates systemic chronic soreness, i.e., at that moment directly linked to metabolic complaints, malignancy and cardiovascular disease (Xiang et al., 2011). The mechanism is shown in Fig. 5.

Fig. 5: Illustration of antagonistic link between the insulin and AMPK pathways- two main metabolic systems of the body.

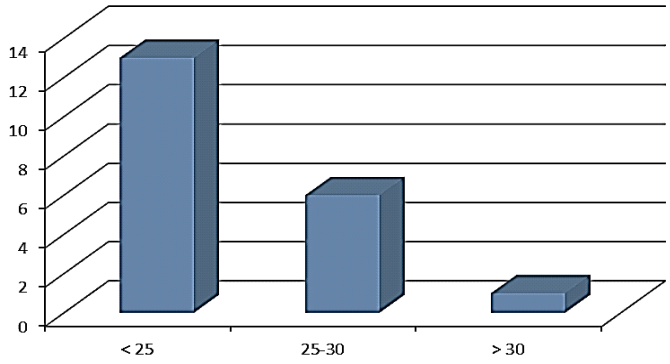


Survey

A survey was conducted among people from area of Township of Lahore in Punjab, Pakistan. We surveyed people from different age groups ranging from 45 to 64 in which people less than age of 45 were in majority. We estimated the body mass index (BMI) in which 13 people had less than 25 and 6 had BMI between 25 and 30 and only one had more than 30 as shown in Fig. 6. Then we surveyed people about regular brisk walking for at least 30 minutes and almost 30% people responded in yes while 70% don't exercise. 80% people had waist less than 94 cm showing the normality of waist in men and women and 5% people had waistline more than 104cm which shows that waist had no direct link with the emergence of disease as shown in Fig. 6.

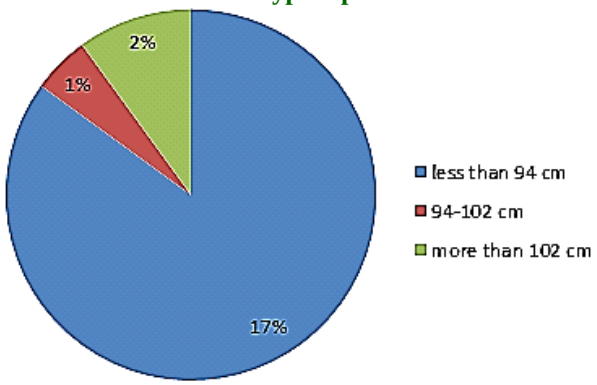
And about 80% people eat healthy fruits and vegetables regularly. Then about 55% people had diabetes type-2 inherited from their blood relations while 45% had no such disease history.

Fig. 6: BMI recorded in 20 patients shows the link of diabetes with the body weight and fatty acid deposited.



This concluded that diabetes type 2 is not necessarily inherited from one generation to the other and regular exercise reduces the risk of fatty acid accumulation, thus decreasing the risk of diabetes type 2. The reason to record BMI and waist measurements was to know whether the deposition of fatty tissues and adipocytes influences the onset of disease or not. And we came to know that people with BMI more than normal had more risk of getting disease despite their non-family disease and fatty acid deposition is directly proportional to glucose intolerance therefore leading to diabetes Type-2 (Fig. 7).

Fig. 7: Survey for the waist showed the link with FFA in diabetes type-2 patients.



Conclusion

Since diabetes type 2 is a major problem in Pakistan and worldwide, the role of Adipocytes and fatty acids in metabolic pathways of glucose intolerance were noted. First the onset of diabetes type 2 was discussed then we talked about the role of adipocytes and how essentially their accumulation led to disease causing symptoms. Then a survey was conducted to know the BMI and waist of people to know the link of fatty acid metabolism with the glucose intolerance. Thus we conclude by saying that adipocytes and FFA play an important and essential role in development of diabetes and insulin intolerance.

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