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Obesity, body fat distribution, insulin resistance and link with type 2 diabetes mellitus

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Abstract- Obesity is associated with insulin resistance and subsequent development of type 2 diabetes mellitus. Usage of measures of obesity including anthropometric parameters and body fat percentage assessment, in general practice is scarce in some counties except for body mass index. Recent studies have demonstrated that indicators of body fat distribution are superior risk indicators of development of insulin resistance compared to indicators of general obesity. Objectives of current review are to evaluate the association of insulin resistance with indicators of body fat distribution and anthropometric markers of general and central adiposity and to establish the association of obesity with insulin resistance and development of type 2 diabetes mellitus. Relevant literature was gathered by searching through electronic data bases. Significant data were extracted and included in to the review. In conclusion, anthropometric markers of obesity among the general population are satisfactory enough to apply in risk assessment of development of obesity associated metabolic disorders including insulin resistance, type 2 diabetes mellitus and will enable with early interventions.

Index Terms- Obesity, Insulin resistance, Type 2 diabetes mellitus, Anthropometry, Body fat percentage

I. INTRODUCTION

"Overweight and obesity are defined as abnormal or excessive fat accumulation in the body that may impair health" [1]. An abnormal growth of the adipose tissue can be due to either enlargement of fat cell size (hypertrophic obesity) or an increase of fat cell number (hyperplastic obesity) or a combination of both [2, 3].

Obesity associated metabolic abnormalities leads to insulin resistance (IR). These metabolic abnormalities including increased non-esterified fatty acid levels and increased triglyceride (TG) levels due to excess lipolysis, cause suppression of glucose uptake by the muscle [4]. Most patients with type 2 diabetes mellitus (T2DM) are obese and if they are not obese they have at least increased percentage of body fat distribution in the abdominal region [4]. The most widely used index to assess the obesity is body mass index (BMI) [5]. Waist circumference (WC), Waist to hip ratio (WHpR) and Waist to height ratio (WHtR) emerged later as markers of central obesity demonstrating to be better correlated with metabolic risk factors than BMI [5].

Later research interests drifted from general obesity to different lipid depots of the body. Methods of Measurement of body composition can be categorized in to two main types. The direct method involves cadaver dissections, which is not very practical in the research field. Therefore, indirect or *in-vivo* methods are used instead. In *in-vivo* methods, body composition is assessed using several formulae or equations using measureable parameters based on the assumption of constant relationships between variables. In the evaluation of body composition, a concept called "body compartments" is used. Generally body can be partitioned as either chemical components (water, fat, minerals) or compartments (e.g. fat mass, fat free mass). Depending on the mode of partitioning, different compartmental methods exist [6].

To measure different fat depots of the body, bio impedance analysis (BIA), dual energy x-ray absorptiometry (DEXA), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and positron emission spectroscopy (PET) techniques are applied [7]. Reference methods of assessing body fat levels are DEXA and Hydro-densitometry [8, 9]. Due to the cost involved and technical difficulties, anthropometric indices still play an important role in assessing body fat distribution as surrogate markers [10].

Although the main effect of the hormone insulin is regulation of glucose and fatty acid metabolic pathways [11, 12], this hormone has other biological actions including vasodilation [12], cardio-protective action [12], anti-apoptosis, platelet inhibition, anti-oxidant, anti-inflammatory, anti-thrombotic, pro-fibrinolytic and anti-atherosclerotic functions [13].

Insulin resistance (IR) is defined as "defect in insulin action resulting in fasting hyper-insulinaemia to maintain euglycaemia" [14]. The ability of insulin to produce the biological action on target tissues, i.e., adipose tissue, skeletal muscle, liver is reduced in individuals with insulin resistance [15]. Genetics, age, acute exercise, physical fitness, dietary habits, medication, obesity and body fat distribution are the factors which influence insulin sensitivity in an individual [16]. Insulin resistance is strongly associated with obesity [17] especially with the central obesity [18] and is a precursor of T2DM and metabolic syndrome [19]. Features of IR include hypertriglyceridemia, increased abdominal, visceral fat and hyper-insulinaemia [4].

Diabetes mellitus (DM) develops as a consequence of interaction of environmental factors with the genetic makeup of a person. The risk of development of DM is intensified with the presence of obesity [16] which is identified as a major risk factor of type 2 diabetes mellitus (T2DM) [20, 21].

II. METHODOLOGY

A. objectives

The Objectives of the current review are to evaluate the association of insulin resistance with indicators of body fat distribution and anthropometric markers of general and central adiposity and to establish the association of obesity with insulin resistance and development of type 2 diabetes mellitus

B. methodology

Relevant evidence for the systematic review was searched using electronic databases including Google scholar, Pubmed, and visually scanning reference lists from relevant studies using Insulin resistance, obesity, BMI, WC, body fat, and diabetes mellitus as keywords. Initially, titles and abstracts were selected which seem to match with the inclusion criteria. At the second stage full papers were screened for relevancy and articles which provided relevant data were included in the review. Related data were extracted using a data extraction format.

III. REVIEW

A. Techniques to assess insulin resistance

There is abundance of techniques used to assess insulin resistance. These can be basically categorized in to two main categories as dynamic tests and single specimen tests. Clamp tests are examples for dynamic tests and the other category includes tests based on biochemical markers on a single specimen which includes homeostatic model assessment (HOMA) [15].

Hyperinsulinaemic euglycemic clamp test is the current gold standard method of insulin resistance assay [19, 22]. Hyperinsulinaemic euglycemic clamp test is time consuming and complex and also requires vast technical expertise. Due to this fact, single specimen tests like HOMA-IR are commonly used and shown to correlate with hyperinsulinaemic euglycemic clamp test. Other than that, Quantitative Insulin Sensitivity Check Index (QUICKI) and beta cell sensory indices like Fasting insulin to glucose ratio (FIGR) and fasting insulin (FI) are used as markers of insulin resistance. Triglyceride to HDL cholesterol ratio can also be used as a marker of insulin resistance which is known to correlate with insulin sensitivity [22].

B. Obesity and insulin resistance

Increased BMI is associated with insulin resistance [23, 24]. However, normal weight individuals may also develop insulin resistance suggesting that whole body adiposity alone may not reveal the risk of development of insulin resistance [23]. Further, it has been demonstrated that IR correlates better with abdominal obesity compared to BMI [23, 24]. Furthermore, regional adiposity measures like volume of visceral (VAT) and subcutaneous adipose tissue (SAT) had shown strong associations with cardiovascular disease risk factors [23].

C. Anthropometric markers of obesity and insulin resistance

Due to difficulties in using some of the methodologies on field, in epidemiological studies, central obesity is determined using either WC, WHR or WTR (waist to thigh ratio) [25, 26]. BMI, WHR and WC of Asians are positively associated with increased fasting insulin levels [27, 28]. Individuals with high Waist to Hip ratios are more insulin resistant compared to individuals with low Waist to Hip ratios [29]. Serum insulin level has a statistically significant positive association with BMI, WC and WHR [27, 30]. But if the pattern of the data indicated in table 1 is followed, it is observed that the association of fasting insulin levels and insulin resistance is strongly associated with BMI and WC compared to WHR [27].

On the other hand, although WHR and WC have shown significant negative correlations with insulin mediated glucose disposal, when these two parameters were analyzed using multiple regression analysis, only WC indicated a significant correlation [31].

When correlations between visceral adipose tissue/ subcutaneous adipose tissue (VAT/SAT) and proinsulin:insulin ratio were analyzed, both BMI and WC have shown similar significance levels [23]. Furthermore other measures of insulin resistance which are indicated in this review are also significantly associated with BMI and WC [23, 32-39]. Insulin sensitivity has a significant negative correlation with BMI and WC [28, 33, 37].

Table 1. Association of Anthropometric markers of obesity with insulin resistance

Reference	Study population	Sample size	Insulin resistant assay method	Results	
				Anthropometric index	Correlation with IR marker (r)
Chung, Cho et al. 2012 [37]	new-onset T2DM subjects	132	HOMA-IR	BMI	0.57 [c]
			ISI	BMI	-0.54 [c]
Miyazaki, Glass et al. 2002 [32]	American T2DM population	30 M	TGD	BMI	0.39 [a]
			EGP×FPI	BMI	0.51[b]
		26 F	TGD	BMI	NS
			EGP×FPI	BMI	NS
Arora, Chen et al. 2016 [39]	newly diagnosed T2DM patients in Qatar	522 (65.9% M)	Logged HOMA2-IR	BMI	0.46 [c]
Preis, Massaro et al. 2010 [23]	USA non-diabetic males and females	3093	Insulin	BMI	0.48 [c]
				WC	0.48 [c]
			Pro-insulin	BMI	0.47 [c]
				WC	0.46 [c]
			HOMA-IR	BMI	0.51 [c]
				WC	0.51 [c]
			Proinsuli:Insulin	BMI	0.31 [c]
				WC	0.30 [c]
Yamada, Moriyama et al. 2012 [38]	A healthy Japanese population	2058 M	HOMA-IR	BMI	0.60 [c]
				WC	0.60 [c]
		1841 F	HOMA-IR	BMI	0.60 [c]
				WC	0.46 [c]
Rutter, Meigs et al. 2005 [33]	UK adults without diabetes or CVDs	2,898	HOMA-IR	WC	0.53 [c]
			$ISI_{0,120}$	WC	-0.31 [c]
Yamada, Moriyama et al. 2012 [38]	Non-diabetic healthy subjects in Japan	2058 M 1841 F	HOMA-IR	BMI	>0.04 [b]
				WC	>0.04 [b]
Farin, Abbasi et al. 2006 [34]	Non-diabetic healthy (mean age 51 years)	139 M 191 F	Steady state plasma glucose concentration	BMI	0.58 [c]
				WC	0.57 [c]
Ying, Song et al. 2010 [36]	Young Chinese females (19-44 years)	1938	HOMA-IR	BMI	0.45 [c]
				WC	0.37 [c]
	Middle aged Chinese females (45-59 years)	1073		BMI	0.50 [c]
				WC	0.45 [c]
Chen, Chuang et al. 2008 [35]	Asian healthy volunteers (22-70 years old)	56 M	Log HOMA-IR	BMI	0.40 [a]
				WC	0.39 [a]
		95 F		BMI	0.60 [a]
				WC	0.64 [a]
Hughes, Aw et al. 1997 [27]	Chinese, Indian and Malay subjects in Singapore	137 Indian M	Fasting insulin	BMI	0.53 [b]
				WC	0.44 [b]
				WHR	0.33 [b]
		147 Indian F		BMI	0.27 [b]
				WC	0.40 [b]
				WHR	0.23 [b]
		122 Malay M		BMI	0.61 [b]
				WC	0.64 [b]
				WHR	0.32 [b]
		118 Malay F		BMI	0.53[NS]
				WC	0.60 [b]
				WHR	0.38 [b]
		142 Chinese M		BMI	0.51 [b]
				WC	0.48 [b]
				WHR	0.30 [b]
		152 Chinese F		BMI	0.30 [b]
				WC	0.40 [b]
				WHR	0.31 [b]

Weyer, Foley et al. 2000 [28]	Pima Indians (diabetics + IGT + NGT)	280	IS	WHR	-0.34 [c]
			Fasting insulin	WHR	0.39 [c]
	NGT pima Indians	172	IS	WHR	-0.22 [b]
			Fasting insulin	WHR	0.34 [c]
Banerji, Faridi et al. 1999 [31]	Asian Indian healthy male	20	IGD	WHR	-0.48 [a]
				WC	-0.63 [b]

M (male), F (female), HOMA-IR (insulin resistance by the homeostasis model assessment), ISI (Insulin sensitivity Index), TGD (Total Glucose Disposal), EGP×FPI [Basal Endogenous Glucose Production × Fasting Plasma Insulin (Hepatic Insulin Resistance)], NS (Not significant)

[a] Significant correlation (P=<0.05)

[b] Significant correlation (P=<0.01)

[c] Significant correlation (P=<0.001)

D. Body fat percentage and insulin resistance

Most commonly used cut off of body fat percentage to define overweight in males is 20.1–24.9% and 30.1–34.9% for females and that for obesity is ≥25% for men and ≥35% for women are applied [40].

Where body fat assessment is concerned, research has mainly targeted on visceral adipose tissue and abdominal subcutaneous adipose tissue levels [41]. Abdominal obesity (upper body obesity) is strongly associated with IR compared to lower body obesity. Abdominal obesity may be due to visceral and/or subcutaneous fat, but many researchers claim that visceral fat is more significant with insulin resistance [42, 43]. Although, abdominal subcutaneous fat volume and visceral fat volume have shown significant relationship with insulin mediated glucose disposal, when multiple regression is applied only visceral adipose tissue has shown a significant relationship with glucose disposal rate [31]. Studies which assess abdominal adiposity using MRI (magnetic resonance imaging), CT (computed tomography) techniques, have been able to come up with the general conclusion that only intra-abdominal and visceral adipose tissue are associated with metabolic abnormalities of obese people compared to subcutaneous adipose tissues [44].

Inter-muscular and thigh subcutaneous adipose tissue (TSAT) depots also have gained research interests [41]. Interestingly, thigh subcutaneous adipose tissue has been identified as a metabolically protective fat depot [41]. A study among overweight and obese subjects has been able to demonstrate a higher degree of insulin sensitivity when the lower VAT and higher TSAT values are present and vice versa [44].

Both SAT and VAT contribute to insulin resistance and associated complications in male African Americans [45]. Although, log insulin values among both African American and Caucasian female groups have shown a correlation with SAT and VAT, only VAT has shown a significant correlation once multiple regression analysis is done [46]. Although insulin, proinsulin, HOMA-IR and Proinsulin:insulin ratio had significant correlations with VAT and SAT, VAT has shown a stronger correlation compared to SAT [23].

Using anatomical landmarks, abdominal subcutaneous adipose tissue can be further divided into two layers [32]. The superficial fascial plane which lies within the subcutaneous adipose tissue separates subcutaneous adipose tissue layer in to superficial and deep layers. Deep subcutaneous fat (DSF) is strongly associated with peripheral insulin resistance compared to superficial subcutaneous adipose tissue. This metabolic difference may be due to arrangement of the tissue layers. Superficial layer is made of small, tightly packed fat lobules while deep layer is made of larger, irregularly distributed lobules [32].

E. Obesity, insulin resistance and subsequent development of T2DM

T2DM develops as a consequence of insulin insensitivity and failure of pancreatic insulin secretion to compensate for reduced insulin sensitivity [48, 49]. According to the findings of United Kingdom Prospective Diabetes Study (UKPDS) a cohort of individuals with recently identified T2DM has shown a gradual decline in β cell function without showing any changes in insulin sensitivity [50]. According to the current knowledge, T2DM only develops in insulin resistant individuals with the onset of β cell dysfunction [48]. When insulin resistance is present due to chronic energy supplementation and obesity, pancreatic beta cells hyper-secrete insulin as a compensatory mechanism to maintain normoglycaemia, Rodent studies have demonstrated that this compensatory insulin hyper-secretion is achieved by expansion of β cell mass and enhanced β cell function. This same pattern is observed in obese subjects compared to non-diabetic lean subjects. Increased blood glucose and free fatty acids act as stimulants for expansion of β cell mass [48].

Table 2. Abdominal fat distribution and insulin resistance

Reference	Study population	Sample size	Abdominal obesity assay method	Insulin resistant assay method	Results	
					Marker of abdominal adiposity	Correlation with IR marker (r)
Després, Lemieux et al. 2008 [44]	Obese premenopausal women	40	MRI	GDR	VAT	0.42 [b]
					SAT	0.01
				GDR	VAT	0.43 [b]
					SAT	0.02
Banerji, Faridi et al. 1999 [31]	Asian Indian healthy male	20	CT	IGD	VF volume	-0.59 [b]
					Abdominal SC fat volume	-0.54 [a]
					Total SC fat volume	-0.49 [a]
					Total body fat volume	-0.56 [a]
Lovejoy, Smith et al. 2001 [46]	Healthy, white pre-menopausal women	103	CT	Log insulin	TAT	0.63 [a]
					VAT	0.57 [a]
					SAT	0.56 [a]
					DSAT	0.54 [a]
					SSAT	0.51 [a]
Lovejoy, Smith et al. 2001 [46]	Healthy, African American pre-menopausal women	55	CT	Log insulin	TAT	0.47 [a]
					VAT	0.41 [a]
					SAT	0.49 [a]
					DSAT	0.39 [a]
					SSAT	0.42 [a]
Tulloch-Reid, Hanson et al. 2004 [45]	African American	36 F	CT	ISI	VAT	- 0.50 [b]
					SAT	- 0.67 [b]
Tulloch-Reid, Hanson et al. 2004 [45]	African American	44 M	CT	ISI	VAT	- 0.47 [b]
					SAT	- 0.57 [b]
Preis, Massaro et al. 2010 [23]	USA non-diabetic males and females	3093	CT	Insulin	SAT	0.41 [c]
					VAT	0.49 [c]
				Pro-insulin	SAT	0.39 [c]
					VAT	0.47 [c]
				HOMA-IR	SAT	0.43 [c]
					VAT	0.52 [c]
				Proinsulin:Insulin	SAT	0.26 [c]
					VAT	0.30 [c]
Miyazaki, Glass et al. 2002 [32]	American T2DM male and female population	30 M	MRI	TGD	TBF mass	- 0.37 [a]
					VAT	- 0.45 [b]
					SAT	- 0.46 [b]
					DSAT	- 0.46 [b]
					SSAT	- 0.39 [a]
				EGP×FPI	TBF mass	0.62 [c]
					VAT	0.32 [a]
					SAT	0.47 [b]
					DSAT	0.49 [b]
					SSAT	0.33 [a]
		26 F		TGD	TBF mass	NS
					VAT	- 0.45 [a]
					SAT	NS
					DSAT	- 0.27 [a]
					SSAT	NS

					TBF mass	NS
				EGP×FPI	VAT	0.39 [b]
					SAT	0.34 [b]
					DSAT	0.41 [c]
					SSAT	NS
Amati, Pennant et al. 2012 [41]	30 to 75 years old sedentary overweight or obese individuals in USA	21 M 31 F	CT	GDR	VAT	-0.37 [b]
					Thigh VAT	0.39 [b]
Yu, Venners et al. 2010 [24]	Pre-diabetic normal weight and overweight rural Chinese females aged 20–60 years	4071	DEXA	HOMA-IR	Percent lower body fat (%LF) Percent trunk fat (%TF)	Both low %LF and high %TF were associated with elevated HOMA-IR. The associations were stronger for higher BMI.
Raji, Seely et al. 2001 [47]	12 Asian Indians and 12 Caucasians with European ancestry	24	CT	GDR	Total abdominal adipose tissue	-0.61 [c]
					Subcutaneous adipose tissue	-0.47 [b]
					Visceral fat level	-0.51 [b]
Weyer, Foley et al. 2000 [28]	Pima Indians (diabetics + IGT + NGT)	280	Hydro densitometry	Insulin sensitivity	BF%	-0.05 [c]
				Fasting insulin level	BF%	0.63 [c]
	NGT pima Indians	172	Hydro densitometry	Insulin sensitivity	BF%	-0.44 [c]
				Fasting insulin level	BF%	0.68 [c]
Chandalia, Abate et al. 1999 [29]	Healthy migrants in USA	29 Caucasians	Hydro densitometry	GDR	BF%	0.65 [c]
		21 Indians	Hydro densitometry	GDR	BF%	0.34[NS]

CT (Computed Tomography), VAT (Visceral Adipose Tissue), SAT (Subcutaneous Adipose Tissue), TAT (Total Abdominal Adipose Tissue), DSAT (Deep Sub-cutaneous adipose tissue), SSAT (Superficial Sub-cutaneous adipose tissue), TBF (Total Body Fat), MRI (Magnetic Resonance Imaging), IGT (Impaired glucose tolerant), NGT (Normal Glucose Tolerant), VF (Visceral fat), SC (Subcutaneous fat)

[a] Significant correlation (P=<0.05)

[b] Significant correlation (P=<0.01)

[c] Significant correlation (P=<0.001)

F. Inflammation and insulin resistance in obesity

Obesity can be described as a state of chronic inflammation, since in obesity inflammatory markers like plasma C-reactive protein (CRP), Interleukin-1 (IL-6) and plasminogen activator inhibitor-1 (PAI-1) are elevated [20] and future development of T2DM can be predicted by presence of inflammation [20].

Chronic activation of innate immune system results in a low grade inflammation in white adipose tissue (WAT) of most obese individuals resulting in IR, impaired glucose tolerance and even diabetes [51]. As a result of inflammation of WAT, production and secretion of a wide range of inflammatory molecules like TNF-α (Tumor necrosis factor- α) and IL-6 (Interleukin-6) are increased and WAT is infiltrated by macrophages [13, 51]. It is presumed that several factors derived from adipocytes and infiltrated macrophages contribute to the pathogenesis of insulin resistance in obesity [13, 51]. Some adipokines [adipocyte secretary products [52]] including TNF-α and IL-6 have the ability to change the insulin sensitivity by triggering some key steps of signaling pathway of insulin [51, 53]. On the other hand, obesity is a well-known independent risk factor of type 2 diabetes mellitus (T2DM) and insulin resistance is the factor which connects the link between obesity and T2DM [20, 51].

Glucose intake can induce acute oxidative stress status for a short period of 3 hours in body and inflammation at the cellular and molecular level in normal people [13, 20]. A meal of mixed fast food also can induce the same reaction [13, 20]. Interestingly, this condition is present in basal fasting state of obese people indicating chronic excess macronutrient intake [13, 20].

G. Storage activity of adipose tissue and insulin resistance

Other than the adipose tissue mass, studies have demonstrated the importance of biological characteristics of adipose tissue in the pathogenesis of insulin resistance [54] and these characteristics include size of adipose tissue, inflammatory properties of adipose tissue and proportion of small adipose cells [54].

It is suggested that ability of adipocyte to store excess triglyceride also plays an important role in systemic insulin resistance [21]. Buffering excess caloric intake by storing it as TG and maintaining lipid and glucose homeostasis are two main functions of adipose tissue [21]. During excessive energy influx, adipose tissue become hypertrophic and adipocyte insulin resistance may develop [21]. This leads to increased lipolysis, leading to decrease in TG storage capacity in the subcutaneous abdominal adipose tissue leading to systemic insulin resistance [21].

Research data suggests that fat cell size also has an independent association with insulin resistance, especially fat cell enlargement in obesity. As a result of reduction in capacity of adipose tissue to store lipids, enlargement of fat cells and ectopic accumulation of lipids ensue [55]. Reduction of storage capacity may be due to failure of differentiation of new fat cells due to genetic abnormalities [55]. A study has demonstrated 2-3 fold decrease in expression in genes related to adipose cell differentiation in an insulin resistant subgroup compared to an insulin sensitive subgroup [56]. It has been demonstrated that subcutaneous and omental fat cell size is associated with insulin resistance in subcutaneous fat cells and whole body insulin resistance in non-diabetic subjects [55].

As mentioned earlier, obesity can result in either hyperplasia of adipose tissue or hypertrophy of adipose tissue [3]. If adipose tissue expansion is due to hyperplasia, it is less likely to develop metabolic abnormalities of the metabolic syndrome [28, 44] including insulin resistance [21]. On the other hand, if adipose tissue becomes hypertrophic due to excess energy influx there is a tendency for the development of insulin resistance [21, 44, 56]. Hypertrophic obesity closely correlates with insulin resistance associated metabolic abnormalities [2, 57] and mean subcutaneous abdominal adipose cell size is associated with insulin resistance and predicts T2DM and this association is independent of BMI or body fat content [2].

A group of healthy first degree relatives of T2DM subjects showed that size of the large adipocyte cells are inversely correlated with insulin sensitivity (R^2=0.534, $p<0.001$). This correlation was intact when corrected for BMI and independent of the gender of the subjects [2]. There was no correlation between insulin sensitivity and the fraction of large adipocyte cells [2] although, a previous study has demonstrated a correlation between insulin sensitivity and fraction of large adipocytes [56]. Furthermore, inflammation in subcutaneous adipose tissue is associated with the proportion of small adipose cells among moderately obese, weight-stable individuals but not with the size of mature adipose cells [54].

H. Type of adipose tissue and insulin resistance

In normoglycemic individuals there is a variability of insulin resistance among group members and about fifty percent of this variability is due to differences in fat mass distribution among each individual [21].

As mentioned earlier, controversy still exists as to whether visceral or subcutaneous fat depots is responsible for development of metabolic abnormalities. Some researchers were able to demonstrate that not only increased visceral fat depots, but also increased subcutaneous adipose tissue is responsible for insulin resistance and glucose disposal[21].

Group of reviewers suggested three possibilities which explain involvement of visceral adiposity in the development of metabolic syndrome. One possibility is that, hyper-lipolytic state of omental adipose tissue exposes the liver to high concentration of free fatty acids through portal circulation [44]. Secondly, Adipose tissue act as an endocrine organ [44, 53]. Thirdly subcutaneous adipose tissue act as a protective metabolic depot and expansion of visceral adiposity suggests relative inability of subcutaneous adipose tissue to provide protective function due to its inability to expand (lipodystrophy) or hypotrophy and this leads to ectopic fat accumulation as well [44].

I. Ectopic fat deposition and insulin resistance

Ectopic fat is defined as “storage of triglyceride (TG) in tissues other than adipose tissue”. Liver, skeletal muscle, heart and pancreas are the sites where this excess TG deposition takes place and these are areas which generally contain only a small amount of fat [58]. These depots can affect cellular function of these organs and are associated with insulin resistance. Increase flux of plasma non-esterified fatty acids (NEFA) to other tissues promotes fat redistribution and ectopic fat deposition when the capacity of adipose tissue to store TG is decreased [21]. As a result of that glucose disposal in skeletal muscle is becoming defective and leads to the development of metabolic syndrome [21].

IV. CONCLUSION

Any defect in insulin signaling pathway can lead to insulin resistance. Alterations in the protein levels and activities of the signaling molecules, enzymes and transcription factors can affect insulin signaling pathway when obesity associated insulin resistance is present. Anthropometric markers of obesity still play an important role in risk assessment of insulin resistance and type 2 diabetes mellitus. These measures are satisfactory enough to apply in risk assessment of general population. Assessment of body fat distribution using modern techniques have been able to aid identifying the pathogenic process of insulin resistance and further development of T2DM and other cardiovascular events. But still, there is more to understand the pathogenic process of this disease since obesity is considered as only one risk factor among many involved in the process. Apart from the body fat content, body fat distribution and different body fat depots, research interests have drifted towards properties of fat cells and ectopic fat distribution in order to understand the pathogenic process of insulin resistance and subsequent development of metabolic syndrome and type 2 diabetes mellitus.Analyze and understand all the provided review comments thoroughly. Now make the required amendments in your paper. If you are not confident about any review comment, then don't forget to get clarity about that comment. And in some cases there could be chances where your paper receives number of critical remarks. In that cases don't get disheartened and try to improvise the maximum.

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