2

Review of Literature

The review of literature pertaining to the study entitled, **"Association of Visceral Adiposity Index and Lipid Accumulation Product with Insulin Resistance among Selected Adult Women and the Impact of Intervention"** is discussed under the following headings:

2.1. Visceral Adiposity and Health

2.2. Visceral Adiposity Indices

2.2.1. Visceral Adiposity Index - An overview

2.2.2. Lipid Accumulation Product - An overview

2.3. Insulin Resistance

2.4. Association of Visceral Adiposity and Insulin Resistance

2.1. Visceral Adiposity and Health

Visceral fat is a type of body fat stored within the abdominal cavity. It's located near several vital organs, including the: liver, stomach and intestines. It can also build up in the arteries. Visceral fat is sometimes referred to as "active fat" because it can actively increase the risk of serious health problems. If you have some belly fat, that's not necessarily visceral fat. Belly fat can also be subcutaneous fat stored just under the skin. Visceral fat is inside the abdominal cavity and isn't easily seen (Gotter, 2021).

A recent report in obese individuals demonstrated that a single measurement of visceral fat (VF) was associated with the risk of dysglycemia, independent of weight or metabolic risk. Visceral adiposity is associated with an adverse cardiometabolic profile, including inflammation, insulin resistance, and myocardial dysfunction—hallmarks of an otherwise "obese" phenotype regardless of adiposity status (Neeland et al., 2012).

Adiposity associated mechanisms that contribute to the development of hypertension are the increase of fat mass (activating the renin-angiotensin-aldosterone system), elevated sympathicotonus, reduced insulin sensitivity, increased blood volume, and intravascular volume, all of them leading to an increase in cardiac output volume (Winter et al., 2013).

An article published by WebMD (2021) stated that Visceral fat is fat that wraps around your abdominal organs deep inside your body. Researchers suspect that visceral fat makes more of certain proteins that inflame your body's tissues and organs and narrow your blood vessels. That can make your blood pressure go up and cause other problems.

Visceral fat can start causing health problems immediately. It can increase insulin resistance, even if you've never had diabetes or prediabetes. Patel & Abate (2013) has found that visceral fat contributes to insulin resistance. Chille (2017) suggested that it's because visceral fat secretes retinol-binding protein 4 (RBP4), a protein that increases insulin resistance.

Visceral tissue in triglycerides is stored as the reservoir of fuel in adipocytes that control glucose homeostasis and lipid metabolism (Heymsfield & Wadden, 2017). In prolonged over-accumulation of triglycerides in adipocytes, the lipid sizes increase, resulting in fat expansion. Excessive lipid accumulation is linked directly with elevated levels of inflammation that may lead to insulin resistance and CVD by the secretion of adipokines (Longo et al., 2019). The existence of low HDL levels and LDL and TG particles are the constituents of the cardiometabolic syndrome (Salazar et al., 2021) (Figure: 1).

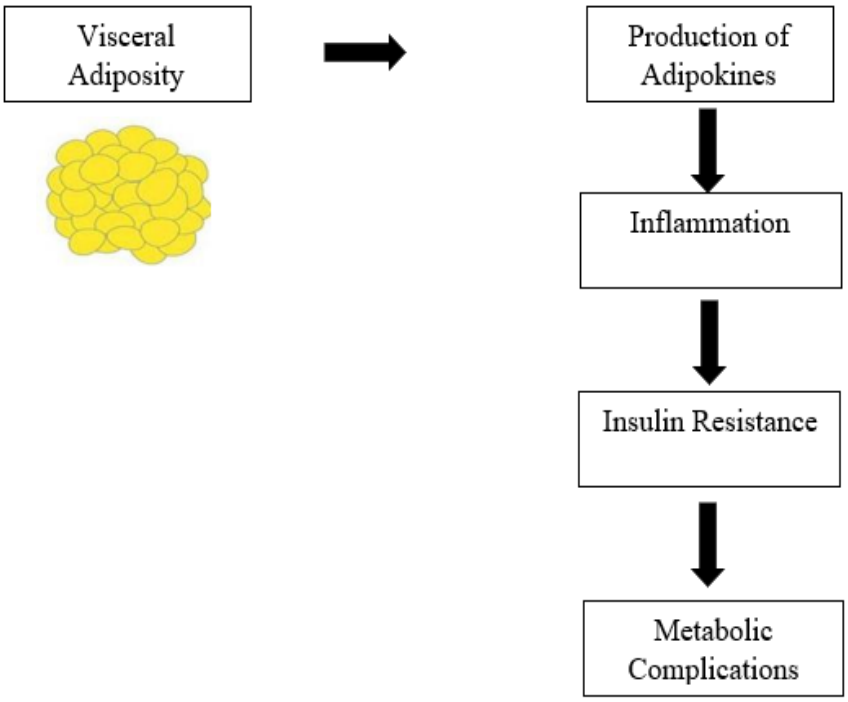


Figure 1: Mechanism of Visceral Adiposity leading to metabolic disturbances

The average ratio of visceral fat to subcutaneous fat at the level of the umbilicus (V/S ratio) in obese subjects is about 0.4. Accordingly, the obese subjects were defined with V/S ratio of ≥ 0.4 as visceral fat obesity, whereas obese subjects with V/S ratio of < 0.4 were considered subcutaneous fat obesity (Matsuzawa, 1987; Fujioka 1987).

Visceral tissue distribution related to geographical distribution is an integral component explaining the relation between adiposity and cardiometabolic risk factors (Leiter et al., 2011). A study which was carried out among non-diabetic Asians aged above 20 years showed that visceral fat was associated with cardiometric risk factors, hence proving the link between visceral fat and development of insulin resistance leading to cardiovascular diseases (Sandeep et al., 201o).

Comparison of the metabolic features of subjects with visceral fat obesity and those with subcutaneous fat obesity showed significantly higher or otherwise greater fasting plasma glucose level, area under the plasma glucose concentration curve after oral glucose loading, triglyceride level, and total

cholesterol level in the former group when either all or sex-matched obese subjects were examined. However, BMI or the duration of obesity was not different between the two groups (Ryo et al., 2014).

Visceral obesity is the most frequently observed component of metabolic syndrome. Metabolic syndrome is a cluster of abdominal obesity, dyslipidemia, hyperglycemia, and hypertension are major public health challenges. The average prevalence of the metabolic syndrome is 31% and is associated with a two-fold increase in coronary heart disease, cerebrovascular disease, and a 1.5-fold increase in the risk of all-cause mortality (Engin, 2017).

Several studies (Grover et al., 2015; Nusselder, 2009; Stenholm et al., 2017; O'Doherty et al., 2016) have documented associations between obesity and major non-communicable diseases risk relative to normal weight using body-mass index (BMI) categories. By contrast, few studies have quantified such associations using absolute metrics such as disease-free years (Nusselder, 2009).

The prevalence and burden of disease resulting from obesity have increased worldwide. Felishbino (2020) attempted to explore the relationship between obesity and disease. Overall, the age-standardized prevalence of obesity in Brazil was higher in females (29.8%) than in males (24.6%) in 2017; however, since 1990, males have presented a greater rise in obesity (244.1%) than females (165.7%). Increases in prevalence burden were greatest in states from the North and Northeast regions of Brazil.

Overall, the burden due to high BMI also increased from 1990 to 2017. In 2017, high BMI was responsible for 12.3% (8.8–16.1%) of all deaths and 8.4% (6.3–10.7%) of total DALYs lost to non-communicable diseases, up from 7.2% (4.1–10.8%), and 4.6% (2.4-6.0%) in 1990, respectively. Change due to risk exposure is the leading contributor to the growth of the BMI burden in Brazil. In 2017, high BMI was responsible for 165,954 deaths and 5,095,125 DALYs. Cardiovascular disease and diabetes have proven to be the most prevalent causes of death, along with DALYs caused by high BMI, regardless of sex or state (Felishbino, 2020).

South Asians are positively related to non-communicable diseases (NCDs). Excess of visceral fat facilitates a high dosage of adipokines in the portal vein to the liver and other body tissues having serious implications in the form of NCDs like diabetes, hypertension, heart diseases, non-alcoholic fatty liver diseases, kidney disease disorders, cancer and other health problems. Abdominal obesity should be addressed before it has progressed further to defined health issues by exercise and diet so that people can live a quality life (Dhawan & Sharma 2020).

Visceral obesity is an adverse form of obesity with serious implications. It is the presence of excess fat deposits in the abdominal region. The latest guidelines for South Asians define abdominal obesity as large waist circumference (WC) ≥90 cm in men and ≥80 cm in women independent of BMI. Abdominal obesity is an indicator of accumulation of triacylglycerols in the liver and muscles; hence; it has been strongly linked to given common NCDs in particular: cardiovascular diseases (CVDs), diabetes, hypertension, cancer, kidney diseases and non-alcoholic fatty liver diseases (NAFLD) (Kesztyüs, 2018).

Visceral fat is the precursor of many non-communicable diseases. The concept of healthy and unhealthy individuals among normal and obese is essential in understanding the underlying cause of metabolic changes' development and progression leading to diseases. As far as the metabolically healthy obese phenotype is concerned, there is a compound interaction between genetic, environmental and behavioral factors (Park et al., 2003). Normal-weight individuals are even at risk if the fat stored in the body is high. The conversion from normal/ obese healthy to unhealthy individuals is effortless if fat is accumulated on the visceral region (Hwang et al., 2015). Therefore, simple tools like VAI are need of the hour for clinical evaluation and better identification of individuals at metabolic complications and risk.

2.2. Visceral Adiposity Indices

2.2.1. Visceral Adiposity Index - An overview

The Visceral Adiposity Index (VAI) has been proposed as a useful tool for early detection of a condition of cardiometabolic risk before it develops into an overt metabolic syndrome. The application of the VAI in particular populations of

women with polycystic ovary syndrome, patients with acromegaly, patients with NAFLD/NASH, patients with HCV hepatitis, patients with type 2 diabetes, and the general population has produced interesting results that the VAI could be considered a marker of adipose tissue dysfunction (Amato & Giordeno, 2014).

The VAI is an empirical index, which includes the anthropometric measurements and biochemical parameters, which have shown to be related to adipose tissue function and express visceral fat distribution (Amato et al., 2010). Due to the outcome of the rising epidemic of cardiovascular mortality, it is timely to understand the body fat distribution, and its clinical implications are crucial.

In a long-term prospective study carried on in Europe, found out that the visceral adiposity index is independently associated with ten years cardiovascular risk, particularly in men and suggests that the VAI can be used as an alternative indicator of long term cardio vascular diseases risk (Kouli et al., 2017).

A study proved that VAI could be used to evaluate adipose tissue dysfunction and associated with cardiometric risk in various patients and showed an existing association of VAI with HOMA-IR (homeostasis model assessment of insulin resistance) (Štěpánek et al., 2019). In a large case-control study, the risk of CVD was elevated with a high VAI value among Chinese men and women (Zhang et al., 2013). The higher VAI values were found to increase the risk of developing the cardiovascular disorder in the future (Agrawal et al., 2019).

Randrianarisoa (2019) showcased additional information as VAI can be used widely to estimate the visceral fat mass and predict subclinical cardiometabolic risk. The patients with ischemic heart failure revealed that visceral adiposity index may be a good predictor of mortality and confirmed more related studies (Vogel et al., 2016).

Dong (2017) stated that the Visceral adiposity index (VAI) is a novel sex-specific index for visceral adipose function; however, the association between VAI and hyperuricemia in China is unknown. VAI was the best predictor for hyperuricemia irrespective of obesity phenotypes, with an area under curve (AUC) ranging 0.665–0.719. The odd ratio (OR) for hyperuricemia in the highest quartile

of the VAI was 6.93 (95% CI 5.79–8.29) after adjusting for age and gender. Following further adjustments for metabolic obesity phenotypes and lifestyle confounders, the ORs were 4.88 (3.92–6.09) and 5.65 (4.68–6.82) according to these two criteria, respectively.

A study in Chennai found the VAI cut-off value 2.69 with a sensitivity of 70.1%, specificity of 74.35%, and AUC of 0.81 with 0.74 to 0.87 95% CI (Munusamy et al., 2015). In a study carried out by Joshi (2018), among young PCOS girls, the cut-off value for PCOS was found to be 2.73, has a sensitivity of 0.76 and specificity of 0.699 and could predict the risk of metabolic syndrome (AOR: 7.757, 95% CI: 2.041-29.48) compared to the literature reference cut-off among the Caucasian population of 1.67.

The visceral adiposity index (VAI), an indirect marker of visceral adipose tissue, serves as a model associated with cardiometabolic risk, but has limitations regarding the Asian population. A new VAI (NVAI) was developed for the Korean population and compared to VAI for the prediction of atherosclerotic cardiovascular disease (ASCVD) risk and development of major cardiovascular diseases (CVD) and stroke (Oh et al., 2018).

Obesity is measured using various methods, for example, waist circumference (WC) measurement or body mass index (BMI), but recently, visceral adiposity index (VAI) has also been utilized to assess obesity and metabolic syndrome better. A study by Akdemir (2019) found out the mean age of the participants was 58.7 ± 8.4 for the ED group and 57.1 ± 7.5 for the control group. The mean VAI was statistically significantly higher in the ED group (5.32 ± 2.77) compared to the control group (4.11 ± 1.93) ($p < 0.001$). Since VAI contains both physical and metabolic parameters, our findings suggest that it discloses the effects of WC, BMI, HDL and TG more clearly. VAI is considered useful for assessing the effect of obesity on ED patients.

Alkhalaqi (2020) study aimed to assess the relative effectiveness of visceral adiposity index (VAI), in comparison with BMI, for T2D among Qatari adults. VAI z-scores showed the strongest association with the risk of T2D (OR, 1.44; 95% CI: 1.24–1.68) and BMI (OR, 1.33; 95% CI: 1.11–1.59). ROC curve

analysis showed that VAI was a stronger predictor than BMI ($P < .0001$). Subgroup analysis indicated that the association was stronger between VAI and T2D in Qatari women than in men. VAI was stronger and an independent predictor of T2D than BAI and BMI among the Qatari adult population.

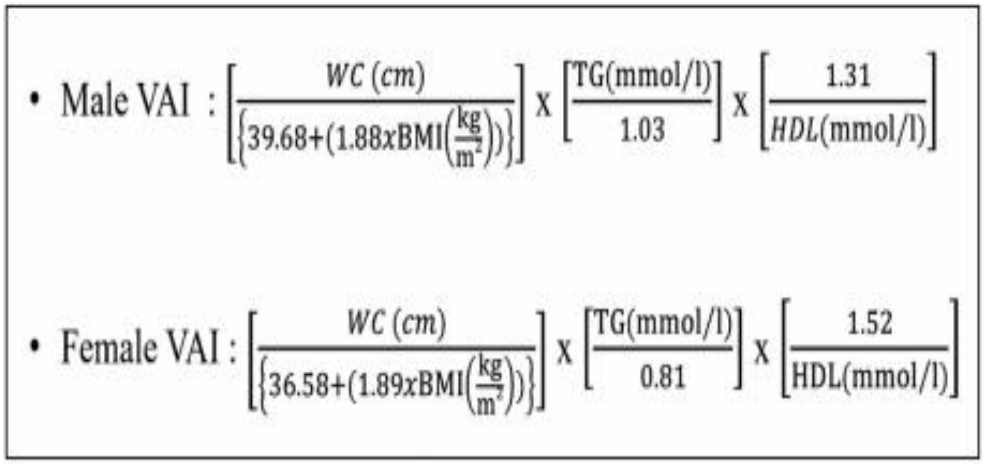
The Visceral Adiposity Index (VAI) is a mathematical model that uses both anthropometric (body mass index [BMI] and WC) and functional (triglycerides [TG] and high-density lipoprotein [HDL] cholesterol) simple parameters. This index, which could be considered a simple surrogate marker of VAD, showed a strong association with both the rate of peripheral glucose utilization (M value) during the Euglycemic-hyperinsulinemic clamp and with visceral adipose tissue (VAT) measured with MRI (Kershaw et al., 2004 & Amato et al., 2010).

(VAI) levels in obese patients with and without metabolic syndrome (MetS) and its relationship with insulin resistance (IR), and define the cutoff value of VAI in the determination of patients with MetS and IR. The cutoff value of VAI in predicting IR was found to be 2.31. While the prevalence of IR was 23.4% in those with a VAI of 2.31, IR frequency in patients equal to or greater than 2.31 was determined as 55%. The study found that MetS was present in almost half of overweight and obese individuals, and the cutoff values of VAI in predicting the presence of MetS and IR were 2.205 and 2.31, respectively.

VAT evaluation can be carried out using an abdominal CT scan or MRI. However, such examinations are quite expensive and are still limited, and therefore difficult to be applied for population-based studies or in clinics. Visceral adiposity index (VAI) is a mathematical model (Fig) to estimate VAT using anthropometric and laboratory parameters by calculating the linear equation of body fat distribution and corrected by high-density lipoprotein cholesterol (HDL-C) and triglyceride level. VAI has been reported to positively correlate with the surface area and volume of VAT (Nusrianto, 2019).

Pathak (2018), in his study, suggested that VAI can replace imaging techniques by reducing the economic burden and can be used among the Indian

population. Many studies have found the supremacy and utility of VAI on other anthropometric indicators (Chen et al., 2015; Choi et al., 2019).



VAI: Visceral Adipose Index, WC: Waist Circumference, BMI: Body Mass Index, TG: Triglyceride, HDL: High Density Lipoprotein

2.2.2. Lipid Accumulation Product

Lipid accumulation product (LAP) is an index that combines waist circumference (WC) and triglyceride (TG), reflecting lipid accumulation. To explore the relationship between LAP and insulin resistance (IR) and to assess whether LAP was superior to WC and body mass index (BMI) in identifying IR. Pearson's correlation analysis done by Xia et al (2012) demonstrated that HOMA-IR was correlated with LAP, BMI, WC, TG, HDL-C and non-HDL-C in both sexes ($P<0.001$). Multivariate analysis demonstrated that LAP had a greater impact on HOMA-IR than BMI and WC. LAP is closely associated with HOMA-IR and is a powerful index that outperforms BMI and WC in identifying IR in non-diabetic individuals.

Lipid accumulation product (LAP) index, a newly developed biomarker of central lipid accumulation, has been proposed as an accurate and independent indicator of the risk of insulin resistance, metabolic syndrome, type 2 diabetes and cardiovascular disease. LAP, which is estimated based on the combination of waist circumference (WC) and triglyceride levels, and is compared to anthropometric measures, including body mass index (BMI), WC, and waist to hip ratio, has recently been considered a better predictor of all-cause and

cardiovascular mortality as well as diabetes development in different ages and ethnic populations (Mirmiran et al., 2014).

Lipid accumulation product (LAP) is a simple and effective indicator of visceral obesity. Song et al (2018) made a study to compare the significance of LAP in predicting hypertension risk with other obesity indices. LAP was significantly different than that of BMI in males ($Z = 2.158, p = 0.0309$) and females ($Z = 3.570, p = 0.0004$), while only performing better in females as compared with that of WHtR ($Z = 2.166, p = 0.0303$). LAP was significantly interacted with family history of hypertension risk both in males (RERI: 1.07, 95%CI: 0.09–2.05; AP: 0.33, 95%CI: 0.23–0.44; SI: 1.92, 95%CI: 1.53–2.41) and females (RERI: 0.80, 95%CI: 0.07–1.53; AP: 0.25, 95%CI: 0.11–0.39; SI: 1.59, 95%CI: 1.16–2.19). However, a significant interaction between LAP and smoking was only observed in males (RERI: 1.32, 95%CI: 0.15–2.75; AP: 0.40, 95% CI: 0.14–0.73).

The LAP value was much higher among Brazilian females at 62.4 ±50.8 (Ferreira et al., 2017). Another conducted among healthy obese postmenopausal women showed that the LAP value was 39.4±30.0 (Lwow et al., 2016). Among GDM women, the LAP value was threefold higher of 133.43 ± 64.02, then healthy pregnant women (Kasirajan et al., 2017). An interesting finding showed that the LAP value among the non-metabolic syndrome group (27.5) was much lower compared to metabolic syndrome chronic kidney individuals (74.6) (Biyik & Guney, 2019).

Chiang & Koo (2012) stated that Lipid accumulation product (LAP) had been advocated as a simple clinical indicator of metabolic syndrome (MS). The prevalence of MS was 19.5 and 21.5% for males and females, respectively. LAP showed the highest prediction accuracy among adiposity measures with an area under the ROC curve (AUC) of 0.901, significantly higher than the adiposity measure of waist-to-height ratio (AUC = 0.813). LAP was a simple and accurate predictor of MS in Taiwanese people aged 50 years and over. LAP had significantly higher predictability than other adiposity measures tested.

The LAP was developed from population-based frequency plots of adult waist circumferences and circulating triglyceride concentrations. With aging, the waist circumference increasingly moves away from its minimal adult value (empirically 65 cm for men and 58 cm for women). The fasting triglyceride concentration likewise departs from its minimal value (theoretically 0 mmol/l). The following simple definitions attempt to describe total-body lipid accumulation: LAP for men = (waist circumference [cm] − 65) × (triglyceride concentration [mmol/l]); LAP for women = (waist circumference [cm] − 58) × (triglyceride concentration [mmol/l]) (Kahn 2003 and Kahn 2005).

A study by Mazidi et al (2018) aimed to examine the association between lipid accumulation product (LAP) and visceral adiposity index (VAI) with dietary pattern (DP) in US adults. The first DP was representative of a diet rich in carbohydrate and sugar, total fat and saturated fatty acid (SFA), high-caloric dietary pattern; the second DP was highly loaded with vitamins, minerals and fiber (nutrient-dense dietary pattern), and the third DP was mainly representative of high dietary polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) (healthy fat DP). The adjusted (age, sex, race, physical activity, smoking, C-reactive protein) mean of LAP, VAI and glucose homeostasis indices increased across increasing quarters of the first DP score (all $P < .001$), while across an increasing score of the second DP, the adjusted mean of LAP, VAI, glucose homeostasis indices decreased.

The lipid accumulation product (LAP) index is computed from waist circumference and triglycerides, representing increased lipo-toxicity. Ayundini et al (2019) aimed to study the relationship between the LAP index and T2DM and its potency as a predictor for T2DM development. Two cross-sectional studies and one cohort study in Japan, USA, and Iran were obtained. In Japan, the cut-off values were different, 21.1 for women and 37.2 for men. A high LAP corresponds to a higher risk of T2DM [19.1 (6.6 – 55.5) for women and 7.4 (5.1 – 10.8) for men]. LAP has a strong association with T2DM, but its ability to predict the incidence of T2DM needs to be confirmed.

Oh (2013), in their study, the lipid accumulation product was calculated using the formula [waist circumference (cm) – 58] × triglycerides (mmol/l). Glucose tolerance status was determined using a 75-g oral glucose tolerance test in 2810 Korean women aged 18–39 years from the general population. Multiple logistic regressions revealed that the lipid accumulation product exhibited a higher odds ratio for abnormal glucose regulation than did BMI after adjusting for age, systolic blood pressure, HDL cholesterol, previous history of gestational diabetes and family history of diabetes (odds ratios 3.5 and 2.6 of the highest vs. the lowest quintiles of lipid accumulation product and BMI, respectively).

Lipid accumulation product (LAP) is an index for the evaluation of lipid accumulation in adults and the prediction of cardiovascular risk considering it a study was made by Olivera et al (2016) LAP was high in most patients (n = 177; 67.3%) and the FGI indicated that 58.5% of the patients (n = 154) had hirsutism. The analysis by LAP quartiles showed a positive correlation (p = 0.04) among patients with a high FGI and an upper quartile LAP (> 79.5) when compared with those with LAP < 29.0 (lower quartile). The study demonstrated an association between high LAP and hirsutism. The FGI could represent a simple and low-cost tool to infer an increased cardiovascular risk in women with PCOS (Olivera et al., 2016)

Cartolano et al (2018) mentioned that Lipid accumulation product (LAP), a simple and low-cost tool, is a novel biomarker of central lipid accumulation and represents a potential surrogate marker for atherogenic lipoprotein profile. LAP was calculated by the formulas [(waist circumference $_{[cm]}$-58) × (triglycerides $_{[mmol/L]}$) for women and (waist circumference $_{[cm]}$-65) × (triglycerides $_{[mmol/L]}$) for men]. The association between LAP and metabolic parameters was tested by a linear trend (general linear model, GLM test) before and after multiple adjustments for potential confounders (sex, age, smoking, statin, fibrate, and hypoglycemic drugs) at a significant level p < 0.05.LAP was positively associated with TC, APO B, NEFA, glucose, insulin and HOMA-IR values and negatively associated with HDL-C. Higher central lipid accumulation

was correlated with a higher percentage of intermediate HDL and small LDL and HDL and less amount of large HDL.

Lipid Accumulation Product (LAP) was proposed as a simple, inexpensive and accurate surrogate index to estimate cardiovascular risk and all-cause mortality. This index combines anthropometric (waist circumference, WC) and biochemical (fasting triglycerides, TG) parameters, connecting anatomical to physiological changes associated with increased central accumulation of lipids in adults (Kahn, 2003).

Kahn (2003) stated that the LAP index evidenced the negative effect of large WC possibly related with small dense LDL, although direct measurement of LDL size has not been done. The validity and superiority of LAP to identify cardiovascular risk, metabolic syndrome, diabetes mellitus and insulin resistance have been compared with body mass index (BMI), WC and waist-to-hip ratio. Despite the negative impact of LAP on glucose metabolism, monitored principally in postmenopausal and polycystic ovary syndrome women, its association with the size of lipoproteins has not been directly evaluated and reported yet (Nascimento et al., 2015).

The lipid accumulation product (LAP) index, computed from WC and serum TG, is thus proposed as a better predictor of MetS as it is a marker of visceral adiposity by Chiang (2012). LAP index has been reported to be a better predictor of diabetes and cardiovascular risks compared to BMI. It has been extensively investigated in polycystic ovarian disease (PCOD) patients, which has emerged as a reliable marker of adverse cardiovascular risk profile.

Associations of BMI, WC, and lipid accumulation product index with metabolic syndrome were compared by multiple logistic regression analysis and receiver operating characteristic analysis (Ray et al., 2018). BMI, WC, and lipid accumulation product index were significantly higher in metabolic syndrome ($P < 0.05$). Although all were independently associated with metabolic syndrome, the lipid accumulation product index had the highest prediction accuracy. The parameter also had a high area under the curve of 0.901 (95% confidence interval 0.85–0.95) and high sensitivity (76.4%), specificity (91.1%), positive predictive

value (88.7%), and negative predictive value (80.9%) for detection of metabolic syndrome.

Spearman's correlation coefficient was used to assess the correlation of the LAP index with the duration of psoriasis and PASI (Ganguly et al., 2018). Logistic regression models were done to assess the risk factors in psoriasis. A statistically significant difference was observed between the LAP index of controls (23.79 ± 13.02) and that of psoriasis patients (46.42 ± 27.2). LAP index was significantly higher in the moderate-to-severe psoriasis group than the mild psoriasis group. LAP index was a significant risk factor associated with psoriasis (OR = 1.07; 95% CI: 1.03 – 1.11).

LAP has a stronger correlation to visceral adiposity, in addition to increased levels of lipolysis and adipocytokines, such as interleukin-6 and of plasminogen activator inhibitor-1. Aging changes body composition, reducing individuals' lean mass and increasing their fat mass, which tends to be redistributed in the body. Consequently, anthropometric measures of central adiposity, such as BMI or abdominal circumference may not be accurate in elderly individuals (Sorkin et al., 1999)

2.3. Insulin Resistance

Insulin resistance is defined as a normal or elevated insulin level that produces an attenuated biological response; (Cefalu, 2001) classically; this refers to impaired sensitivity to insulin-mediated glucose disposal. Compensatory hyperinsulinemia occurs when pancreatic β cell secretion increases to maintain normal blood glucose levels in the setting of peripheral insulin resistance in muscle and adipose tissue.

Insulin resistance syndrome refers to the cluster of abnormalities and related physical outcomes that occur more commonly in insulin-resistant individuals. Given tissue differences in insulin dependence and sensitivity, manifestations of the insulin resistance syndrome are likely to reflect the composite effects of excess insulin and variable resistance to its actions (Reaven 2004).

Insulin resistance exists when a normal insulin concentration produces a less than normal biological response. The ability to measure insulin resistance is important to understand the etiopathology of Type 2 diabetes, examine the epidemiology, and assess the effects of the intervention. Researchers assess and compare measurement methods and have undertaken a literature review from 1966 to 2001. Quantitative estimates of insulin resistance can be obtained using model assessments, clamps or insulin infusion sensitivity tests. There is considerable variation in the complexity and labor intensity of the various methods.

The concept of IR was proposed as early as 1936 and is generally defined as decreased sensitivity or responsiveness to the metabolic actions of insulin, such as insulin-mediated glucose disposal and inhibition of hepatic glucose production. IR is probably the unifying pathophysiological denominator of a cluster of non-communicable disease risk factors, including elevated plasma glucose, lipid regulation problems (elevated triglycerides increased small low-density lipoproteins and decreased high-density lipoproteins), hypertension and obesity. This combination is referred to as either “the metabolic syndrome (MS)” or “syndrome X” or “IR syndrome.”

Insulin resistance occurs as part of a cluster of cardiovascular-metabolic abnormalities commonly referred to as “The Insulin Resistance Syndrome” or “The Metabolic Syndrome.” This cluster of abnormalities may lead to type 2 diabetes, accelerated atherosclerosis, hypertension, or polycystic ovarian syndrome depending on the individual's genetic background developing the insulin resistance. In this context, insulin resistance should be defined as a disease entity that needs to be diagnosed and treated with specific drugs to improve insulin action (Lebovitz, 2001).

Insulin is an endocrine peptide hormone that binds plasma membrane-bound receptors in target cells to orchestrate an integrated anabolic response to nutrient availability. In all animals, insulin or insulin-like peptides (ILPs) have been identified. ILPs provide mitogenic signaling input invertebrates, but their effects on metabolic processes and fuel selection are less significant.

Leveraging gene duplication events through evolutionary time, mammals developed specialized functions for the related peptide hormones insulin, insulin-like growth factor (IGF)-1 and IGF-2, IGF-1 and IGF-2 promote cell growth and differentiation in mammals; in contrast, insulin primarily controls metabolic fluxes. However, the blurriness of these functional distinctions is highlighted by the high homology between the insulin and IGF-1 receptors, which form hybrid heterodimers in many cell types and share many downstream effectors.

The overlap in signaling functions between insulin and IGF-1 likely also contributes to the well-established relationship between hyperinsulinemia and several cancers. The focus was on the physiological effects of mammalian insulin binding to the insulin receptor and molecular mechanisms by which insulin's effects are attenuated in the insulin-resistant state that heralds and accompanies T2D (Petersen & Gerald, 2018).

As obesity and diabetes reach epidemic proportions in the developed world, the role of insulin resistance and its consequences are gaining prominence. Understanding the role of insulin in wide-ranging physiological processes and the influences on its synthesis and secretion, alongside its actions from the molecular to the whole-body level, has significant implications for many chronic diseases seen in Westernized populations today. Rapid globalization, urbanization and industrialization have spawned epidemics of obesity, diabetes and their attendant co-morbidities, as physical inactivity and dietary imbalance unmask latent predisposing genetic traits (Wilcox, 2005).

Banerjee et al (2014) said Insulin resistance (IR), as a result of unhealthy lifestyles and westernization, most likely contributes to the increased incidence of metabolic abnormalities and, consequently, the development of metabolic syndrome (MS). Anthropometric profile, lipid profile, fasting blood glucose, C-reactive protein (CRP) and C-peptide of 112 individuals were measured using the standard procedures. IR was assessed using the homeostasis model (Homeostatic model assessment [HOMA]-IR). The mean IR was 1.5 (1.0).

Individuals with MS, higher body mass index and CRP ≥6 mg/l had higher IR. Linear regression showed that among MS components, waist circumference had the highest contribution toward IR. The optimal cut-off value to detect IR by HOMA2-IR was 1.35. IR was found to have a strong association with various clinical-metabolic risk factors.

Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as it does in a normal population. Insulin action results from insulin binding to its plasma membrane receptor and is transmitted through the cell by a series of protein-protein interactions (Lebovitz, 2001).

Two major cascades of protein-protein interactions mediate intracellular insulin action: one pathway regulates intermediary metabolism, and the other plays a role in controlling growth processes and mitoses. The regulation of these two distinct pathways can be dissociated. Several mechanisms have been proposed as possible causes underlying the development of insulin resistance and insulin resistance syndrome. These include:

(1) Genetic abnormalities of one or more proteins of the insulin action cascade

(2) Fetal malnutrition

(3) Increases in visceral adiposity.

Type 2 diabetes mellitus (T2D) is one of the defining medical challenges of the 21st century. Overconsumption of relatively inexpensive, calorically dense, inadequately satiating, highly palatable food in industrialized nations has led to unprecedented increases in obesity. In the United States, the combined prevalence of diabetes and prediabetes is over 50%.

Although only a subset of obese people develops T2D, obesity is a major risk factor for T2D, and rates of T2D prevalence have paralleled those of obesity. The fasting hyperglycemia that defines T2D is largely secondary to insulin's inadequate action of the major glucose-lowering hormone. Understanding the

mechanisms of insulin action is therefore essential for the continued development of effective therapeutic strategies to combat T2D (Petersen & Gerald, 2018).

The relative roles of obesity, insulin resistance, insulin secretory dysfunction, and excess hepatic glucose production in developing non-insulin-dependent diabetes mellitus (NIDDM) are controversial. A prospective study determined the factors that predicted the development of the disease in a group of Pima Indians. A body-composition assessment, oral and intravenous glucose-tolerance tests and a hyperinsulinemic-euglycemic clamp study were performed in 200 non-diabetic Pima Indians (87 women and 113 men; mean [±SD] age, 26 ±6 years).

Insulin resistance is accepted to be a major risk factor in the etiology of type 2 diabetes mellitus, hypertension, dyslipidemia, atherosclerotic vascular disease, and may be a risk factor for coronary heart disease and stroke as well. Several risk factors(e.g. obesity, physical inactivity, body fat distribution, age and hyperinsulinemia) may be considered markers of insulin resistance. Insulin resistance is a predictor for Type 2 diabetes mellitus even in individuals with normal glucose tolerance. Therefore, it is important to recognize insulin resistance in the pre-disease stage when therapeutic intervention is more successful than the manifest disease.

Insulin resistance is one pretty troublesome entity that very commonly aggravates metabolic syndrome. Many methods and indices are available for the estimation of insulin resistance. It is essential to test and validate their reliability before investigating patients. At present, hyperinsulinemic-euglycemic clamp and intravenous glucose tolerance test are the most reliable methods for estimating insulin resistance and were used as a reference standard.

Some simple methods from which indices can be derived have been validated, e.g., homeostasis model assessment (HOMA) quantitative insulin sensitivity check index (QUICKI). For the clinical uses, HOMA-insulin resistance, QUIKI, and Matsuda were suitable, while HES, McAuley, Belfiore, Cederholm, Avignon and Stumvoll index were suitable for epidemiological/research purposes.

With an increasing number of these available indices of IR, it may be difficult for clinicians to select the most appropriate index for their studies (Gutch et al., 2015).

The most well-established methods are the euglycaemic clamp, minimal model assessment and homeostatic model assessment (HOMA). No single test is appropriate under all circumstances. Several well-established tests are used to measure insulin resistance: the choice of method depends on the size and type of study to be undertaken.

Although the so-called 'gold-standard' test, the euglycaemic clamp, is useful for intensive physiological studies on small numbers of subjects, a simpler tool such as HOMA is more appropriate for large epidemiological studies. It is important to be aware that most techniques measure stimulated insulin resistance, whereas HOMA estimates basal insulin resistance. Caution should be exercised when comparing studies due to variations in infusion protocols, sampling procedures and hormone assays used in different studies (Wallace, 2002).

Homeostasis model assessment was first developed in 1985 by Matthews et al. It is a method used to quantify insulin resistance and beta-cell function from basal (fasting) glucose and insulin (or C-peptide) concentrations. HOMA is a model of the relationship of glucose and insulin dynamics that predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and β-cell function.

Insulin levels depend on the pancreatic β-cell response to glucose concentrations, while glucose concentrations are regulated by insulin-mediated glucose production via the liver. Thus, deficient β-cell function will echo a diminished response of β-cell to glucose-stimulated insulin secretion. Similarly, insulin resistance is reflected by the diminished suppressive effect of insulin on hepatic glucose production.

The HOMA model has proved to be a robust clinical and epidemiological tool for assessing insulin resistance. HOMA describes this glucose-insulin homeostasis utilizing a set of simple, mathematically-derived nonlinear equations. The approximating equation for insulin resistance has been simplified; it uses a

fasting blood sample. It is derived from using the insulin-glucose product, divided by a constant. FPG × FPI is a hepatic insulin resistance index (Matthews et al., 1985). It is appropriate to apply this index in large epidemiological studies where only fasting insulin and glucose values are available.

It is derived from the product of the insulin and glucose values divided by a constant that is, calculated by using the following formula: fasting glucose (mg/dL) X fasting insulin (μU/mL) / 405 (for SI units: fasting glucose (mmol/L) X fasting insulin (μU/L) / 22.5). A value greater than 2 indicates insulin resistance. There is a small difference in cut-off values of HOMA-IR in various studies. Some studies have suggested the normal cut-off value to be 1.85 and also suggested that The threshold levels must be modified by age in the non-diabetic population (Dua et al., 2014).

The utility of HOMA-IR in assessing Insulin resistance has been validated even in the pediatric age group and adolescents. HOMA-IR is a simple and non-expensive method for the evaluation of insulin sensitivity. It has a good correlation with the results of the glucose clamp test in subjects with mild diabetes without significant hyperglycemia.

The limitation of HOMA-IR is that it is difficult to be used in patients who have received insulin for any reason. Moreover, its use is controversial in patients with poor glycemic control and inpatients with severe β cell dysfunction (Gutch et al., 2015). Insulin resistance due to any cause like metabolic syndrome, hypertension, hyperlipidemia, coronary artery disease, hepatic dysfunction the polycystic ovary syndrome may manifest as increased HOMA-IR values (Unger, 2003).

Early treatment of hyperglycemia, hyperlipidemia and other metabolic irregularities reduces the cardiovascular risk in these patients. But these benefits are usually denied to patients mainly due to delay in diagnosis. Many patients admitted with myocardial infarction are diagnosed with type 2 diabetes while in intensive care units for myocardial infarction.

Unlike in type I diabetes mellitus, where insulin is deficient consequent to immune-mediated destruction of B cells, in type 2 diabetes, there is insulin resistance. Insulin resistance in pre-diabetic stages can be diagnosed by using various methods. Some simple methods from which indices can be derived have been validated (Bhosle et al., 2016).

2.4. Association of Visceral Adiposity and Insulin Resistance

The association between abdominal fat accumulation and the risk of chronic diseases, including type II diabetes and coronary heart disease, has long been recognized. Insulin resistance may be a key factor in this link. Subcutaneous fat probably plays a major role in determining systemic plasma non-esterified fatty acid concentrations relevant to insulin resistance. In conclusion, there is no proof of a causal link between visceral fat accumulation and insulin resistance or the associated metabolic syndrome (Frayn, 2000).

There is considerable variability in the relationship between insulin sensitivity and regional fat depots in humans. It could be due to technical issues related to measuring the visceral fat depot and variability in the relationship between its size and lipolytic activity. The latter phenomenon could occur, for example, if a given fat depot contained fewer adipocytes of larger size in one subject than in another. One would expect greater lipolysis and greater resistance to the antilipolytic effect of insulin when fat cells are larger and fewer in number (Ravussin, 2002).

However, several studies have demonstrated that subcutaneous fat, not visceral fat, is the best predictor of insulin resistance in obese individuals (Frayn, 2000). The factors responsible for these inconsistent results have yet to be elucidated. One potential explanation for these discordant reports is the failure to account for gender differences.

Another potential explanation for the discordant reports might be the failure to account for the differences in the individual body type of the study subject. All previous studies investigating the association between abdominal fat

distribution and insulin resistance evaluated the subcutaneous and visceral fat area and volume. Still, these values were not related to the body type of each subject (Miyazaki & DeFronzo, 2009).

The possible links between routinely available body adiposity parameters and diabetes and insulin resistance development were done by (Sun et al., 2019). An examination was performed a population-based cross-sectional study in 9496 subjects aged 40 years, or older LAP provided the best discrimination accuracy for diabetes [area under the curve (AUC): 0.658 95% confidence intervals (CI) 0.645–0.671] and insulin resistance (AUC: 0.781 95% CI 0.771–0.792) when compared with other body adiposity parameters. The LAP index seems to be a better indicator than other adiposity measures tested in the study to evaluate the association of visceral fat mass with diabetes and insulin resistance, which should be given more consideration in clinical practice.

Visceral fat is now recognized to have metabolic, endocrine, and immune functions; increased visceral adiposity enhances the risk of metabolic and cardiovascular disorders. Potential mechanisms of this increased risk may include increased free fatty acid release and alterations in adipokines. Lifestyle interventions resulting in weight loss and loss of visceral fat can significantly impact cardiometabolic risk. Bariatric surgery has also been shown to improve insulin resistance, type 2 diabetes, and other comorbidities of obesity. Several medical therapies for type 2 diabetes or obesity also promise to impact visceral adiposity-related comorbidities (Griffith et al., 2010).

Morshed et al (2021) said that VAI had predictive association with prediabetes [OR (95% CI: 9.504 (2.173, 41.576); p = 0.03] and high insulin resistance (HOMA-IR ≥ 2.6) in females with prediabetes [OR (95% CI) = 3.50 (1.476, 8.297); p = 0.004] only. It could satisfactorily discriminate prediabetes in both sexes (male: AUC = 0.767, p = 0.001; female: AUC = 0.641, p < 0.001) and high insulin resistance in females with prediabetes (AUC = 0.641; p = 0.019) only. So, VAI was associated with prediabetes and insulin resistance only in females with prediabetes.

At baseline, VAT and insulin sensitivity differed significantly by MetS status and BMI category. VAT and homeostatic model assessment of insulin resistance (HOMA-IR) at baseline (VAT odds ratio [OR] = 1.16 [95% CI: 1.12-2.31]; HOMA-IR OR = 1.85 [95% CI: 1.32-2.58]) and increases over time (VAT OR = 1.55 [95% CI: 1.22-1.98]; HOMA-IR OR = 3.23 [95% CI: 2.20-4.73]) were associated with incident MetS independent of BMI category. Differing levels of VAT may be driving metabolic heterogeneity within BMI categories. Both overall and abdominal obesity (VAT) may play a role in the development of MetS. Increased VAT over time contributed additional risk (Chaffin et al., 2021).

A cross-sectional study was carried out by Moon et al (2019) said that insulin resistance, compared with individuals with the highest adiponectin levels and visceral fat mass < 75th percentile, the fully adjusted odds ratios (ORs) for HOMA-IR ≥ 2.5 and Matsuda index < 25th percentile were 13.79 (95% confidence interval, 7.65–24.83) and 8.34 (4.66–14.93), respectively, for individuals with the lowest adiponectin levels and visceral fat ≥ 75th percentile. Regarding β-cell dysfunction, the corresponding ORs for HOMA-β < 25th percentile, insulinogenic index < 25th percentile, and disposition index < 25th percentile was 1.20 (0.71–2.02), 1.01 (0.61–1.66), and 1.87 (1.15–3.04), respectively. Low adiponectin levels and high visceral adiposity might affect insulin resistance and β-cell dysfunction.

Castro et al (2014) stated that insulin resistance (IR) is one of the main culprits in the association between obesity, particularly visceral, and metabolic and non-metabolic diseases. The current pathophysiological and molecular mechanisms were highlighted and possibly involved in the link between increased VAT, ectopic fat, IR and comorbidities.

Jung et al (2019) examined whether visceral adiposity is a risk factor for colorectal cancer (CRC) and colorectal adenomas. The mean areas of visceral adipose tissue (VAT) areas in control, adenoma, early- and advanced-stage CRC groups were 94.6, 116.8, 110.4, and 99.7 cm^2, respectively (P<0.001). The risk of adenoma positively correlated with VAT area and the visceral-to-total fat ratio (P for trend <0.01), but the risk of CRC did not (P>0.05).

The risk of both adenoma and CRC positively correlated with fasting plasma glucose levels (*P* for trend <0.05). In patients with early-stage cancer (n=17), VAT area decreased when the CT scan at diagnosis was compared with that taken before the diagnosis of CRC, but superficial adipose tissue area did not, so visceral-to-total fat ratio significantly decreased (46.6% vs. 50.7%, respectively, *P*=0.018)

Mutsert et al (2018) stated that abdominal obesity is a well-established risk factor for the development of type 2 diabetes. However, sex differences may exist. Study found that Participants had a mean [standard deviation (SD)] age of 56 (6) years, body mass index: 25.9 (3.9) kg/m^2, VAT: 89 (55) cm^2, and SAT: 235 (95) cm^2. In the multivariate models in men, per SD of VAT, the homeostatic model assessment of insulin resistance (HOMA-IR) was 20% (95% CI: 14–26) higher, and per SD SAT 21% (15–27) higher. In women, per SD of VAT, the HOMA-IR was 40% (29–52) higher and 12% (6–19) higher per SD SAT. Associations with measures of insulin secretion were weaker than with insulin resistance.

Morshed et al (2021) found that people with prediabetes had significantly higher median value of VAI {3.08 (2.26) vs. 1.86 (2.31); p < 0.001} with higher frequency of high VAI (>1) (98.3% vs. 85.8%; p < 0.001) than the control population. HOMA-IR level was significantly higher in prediabetes with high VAI (cut-off of 2.64) than control with normal VAI [2.78 (2.22, 4.15) vs. 2.20 (1.53, 3.36); p = 0.002]. VAI was positively correlated with HOMA-IR in females with prediabetes (r = 0.299, p = 0.003).

VAI had predictive association with prediabetes [OR (95% CI: 9.504 (2.173, 41.576); p = 0.03] and high insulin resistance (HOMA-IR ≥ 2.6) in females with prediabetes [OR (95% CI) = 3.50 (1.476, 8.297); p = 0.004] only. It could satisfactorily discriminate prediabetes in both sexes (male: AUC = 0.767, p = 0.001; female: AUC = 0.641, p < 0.001) and high insulin resistance in females with prediabetes (AUC = 0.641; p = 0.019) only. So, VAI was associated with prediabetes and insulin resistance only in females with prediabetes.

Sawant et al (2017), in their research, identified that HOMA-IR, TyG and frequency of MS were significantly higher in the patients' group ($p < 0.0001$ for each) in comparison to controls. In HCV patients, increased fasting blood glucose (FBG) was the only strong predictor of severe hepatic necro-inflammation. High FBG, older age, female sex, high AST, TyG, VAI, serum lipids abnormalities and presence of MS were all associated with severe fibrosis on univariate regression analysis.

Only high AST, TyG, VAI and LDL were independent predictors of severe fibrosis. A model using the four parameters showed a strong validity in predicting advanced hepatic fibrosis (AUC 0.801; CI: 0.705 - 0.897, $p < 0001$). Female sex, high BMI, VAI, LDL, and TG values are all significantly associated with moderate/severe steatosis on univariate analysis. High BMI and LDL are the strong predictors (AUC 0.738; CI 0.625 - 0.851, $p = 0.002$).

A total of 439 individuals were included in the study, of which 269 had DM, and 170 were healthy volunteers, and the mean age was 41.47±6.82 and 36.16±7.44 years, respectively (Parveen et al., 2020). More people with diabetes had high VAI (86.5% vs. 98.9%) and high IR (43.5% vs. 85.1%) than healthy controls. The highest sensitivity and specificity were found at a cut-off of 2.23 of VAI, while 3.65 had the highest specificity. Insulin resistance was observed significantly higher in those with diabetes than control, both in the case of normal and high VAI at all cut-offs of VAI. Among anthropometric parameters (WC, BMI and VAI), VAI had a positive ($r=0.21$, $p<0.001$) correlation with HOMA-IR than WC ($r=0.10$, $p=0.043$). Visceral fat was linearly related to insulin resistance (ß=0.18, $p<0.001$). The area under the curve (AUC) (0.66) showed that VAI could discriminate HOMA-IR.