Chapter One

Review of Literature
1.1. ACANTHOSIS NIGRICANS

Acanthosis nigricans (AN) refers to a roughness and velvety thickening of the skin with hyperpigmentation commonly seen on the axillae, groin, sub-mammary region, and back and sides of the neck (1). AN is characterized by a light brown to black thickened areas of skin, usually seen on the nape of the neck and axillae. The area appears dirty with a rough texture, and will not scrub or peel off (2). Villas et al., in 2000 suggested that AN is more frequently present than anticipated and can be used as a marker for future risk.

AN is a skin marker for hyperinsulinemia. It is indicative of an underlying insulin resistance (IR). IR has the propensity to develop into Type 2 Diabetes Mellitus (T2DM) and also leads to obesity. AN targeted screening is recommended for detection of early IR through visual inspection for AN, thanks to its non-invasive nature (3).

Fasting serum insulin when raised, is accompanied by AN on the skin. A study conducted in Japan by Yamazaki et al, over ten years; concluded that AN could be a reliable cutaneous marker for IR and that children with AN had significantly more insulin resistance than those without (4). The prevalence of AN is high in India and is an independent cutaneous marker of both Type 2 diabetes and increased body mass index (BMI) (5).

Acanthosis Nigricans (AN) as a skin problem was first documented by Unna and Pollitzer in 1889. Its association with Insulin Resistance (IR) was identified almost a century later in 1976 by Kahn et al. and in the year 2000 the America Diabetes Association declared it as a risk factor for the development of Diabetes Mellitus in children (6).

The skin possesses specific hormone receptors and produces various hormones (7). As a consequence, many endocrine disorders manifest themselves as skin afflictions. The association of Acanthosis nigricans, skin tags, diabetes mellitus due to insulin resistance, and obesity in adolescents and young adults represents a well-defined syndrome.
Hyperandrogenism may also be present. Insulin and insulin-like growth factor-1, and their receptors on keratinocytes are involved in the complex regulations leading to the peculiar epidermal hyperplasia. This condition is unrelated to other types of AN (8).

AN, is a dermatosis characterized by velvety, brown to black, hyperkeratotic plaques, typically of the flexures, (9-12). AN is associated with malignancy, obesity and insulin resistance among many others. The dark colour of AN is likely due to hyperkeratosis rather than to a mild increase in melanin pigmentation (13). The recognition of this condition is essential for prevention of disease progression to Type 2 diabetes, the metabolic syndrome, and diagnosis of polycystic ovary syndrome (14) (15-18).

Cutaneous involvement is localized but not well circumscribed, since it blends imperceptibly into surrounding skin at the edges. Less commonly involved is the face, the inner thigh, antecubital and popliteal fossae, the umbilical region, eyelids, knuckles, palms, soles, nipples, and areolae (9). The lips and mucous membrane of the mouth, upper respiratory tract, and vagina are affected in unusual cases. In severe cases, diffuse hair loss and nail dystrophy may occur. Clinically, the neck is the most easily accessible area (18).

Skin colour may influence the presence of AN as a predictor of IR. Taking into consideration Phototypes I-VI of Fitzpatrick and Burke’s quantitative scale of AN, people with skin phototype IV have a high frequency of AN on the neck, compared with those with phototypes II and III. (19). AN and skin tags are markers of hyperinsulinemia and IR in individuals with Obesity (8, 9). The prevalence of AN is influenced by the race, and obesity increases the risk (18). Fasting insulin concentrations were two fold higher in subjects with AN. It was concluded that AN presence suggests IR and thus helps identify those with the highest risk for non-insulin-dependent diabetes mellitus in this population (20).
Medications that promote hyperinsulinemia, such as glucocorticoids (9), niacin (21), simvastatin and other lipid lowering agents, insulin, oral contraceptives and protease inhibitors (22) can cause AN. If such a cause is suspected the offending drug should be withdrawn.

In a recent study, IR was compared in obese women with and without AN. This was a cross-sectional study. IR was determined using homeostasis model assessment. Glucose tolerance test also was performed for all of participants. No Patient without AN had insulin resistance (23).
HISTORY

Acanthosis Nigricans (AN) is a well-established cutaneous marker for IR. AN was first documented by Unna and Pollitzer in 1889 and its association with IR was identified a century later in 1976 by Kahn et al. It was added to the list of markers, for risk of Diabetes in post pubertal, overweight youth in 2000 by the American Diabetes Association (ADA) (24).

Fig 1.1: Grades of Acanthosis nigricans on the neck.
1.1.1. HISTOPATHOLOGY OF ACANTHOSIS NIGRICANS

Histopathological examination shows a mammillated, acanthotic epidermis with ortho-hyperkeratosis, and no significant inflammatory infiltrate.

- Papillomatosis- upward projection of finger-like dermal papillae covered by thinned epidermis.
- Epithelium in ‘valleys’ between papillary projections: mild acanthosis & hyperkeratosis.
  Hyperpigmentation of basal layer: resulting largely from hyperkeratosis.
- Sometimes - hypertrophy of all layers of epidermis may be seen, similar to epidermal nevi or seborrheic keratosis.
- Usually no dermal inflammation.
- Oral lesions show thickening of epithelium with: papillary hyperplasia & Acanthosis.
- Superficial resemblance to condyloma acuminatum (25).

Fig : 1.2 Histopathology of AN H&E stain
The term "acanthosis" is actually a misnomer, as the actual amount of thickening of the malphigian layer, is mild (12). An infiltrate of lymphocytes, plasma cells, or neutrophils may be present (9).

1.1.2. PATHOGENESIS OF ACANTHOSIS NIGRICANS

Hyperinsulinemia refers to raised levels of serum insulin. IR can be due to:

- pre receptor defect - due to anti insulin antibodies,
- receptor defect - due to reduced number of receptors, or
- post receptor defect - due to abnormal transduction of signals or reduced sensitivity of the peripheral tissues to insulin (obesity).

IR leads to excessive amounts of free serum insulin which interacts with insulin-like growth factor-1 (IGF-1) and its receptors (IGFR) in peripheral tissues and hence increases their binding. This boosts the proliferation of keratinocytes and fibroblasts(8). Defects in fibroblast growth factor receptor type 2 and 3 are also involved in the pathogenesis of AN (10).

A resistance to the uptake of insulin leads to an elevated levels of serum insulin. Hyperinsulinemia, is associated with elevations in the serum concentrations of free insulin-like growth factor (IGF-1) and reduced levels of IGF-binding protein 3 (IGFBP-3). Binding of the excess IGF-1 to the free insulin receptors on keratinocytes causes epidermal hyperplasia which manifests as cutaneous papillomas, skin tags or AN.

IGFBP-3, is a ligand for the nuclear retinoid X receptor alpha, which may decrease the transcription of anti-proliferative genes which are normally activated by the body's endogenous
retinoids (26). Insulin-mediated reductions in IGFBP-3, also promote keratinocyte proliferation which may lead to AN and skin tags.

In obese patients, with elevated plasma levels of testosterone the IR is due to dysfunctional insulin receptors (8, 9). In Polycystic Ovarian Syndrome also the insulin receptors are defective leading to IR (27-29).

When the secreted Insulin is unable to keep the serum glucose levels under control Diabetes Mellitus sets in. Obesity is frequently associated with elevated plasma levels of free fatty acids, which induce insulin resistance through inhibition of glucose transport activity. The role of various cytokines secreted by the adipocytes, named adipokines (leptin, resistin, adiponectin, etc.), has been also recently emphasized (30).

The insulin receptor is a tyrosine-specific protein kinase which is activated on insulin binding resulting in auto-phosphorylation of the receptor. This is an early step in the transmembrane signalling produced by insulin. In patients with IR & AN, erythrocytes and cultured fibroblasts exhibited normal insulin binding. Receptors extracted from erythrocytes also exhibited normal insulin binding. Receptors from the patient's fibroblasts exhibited a decrease in their ability to phosphorylate exogenous substrates. The IR can thus be due to a genetic abnormality (31).

The presence of insulin receptor antibodies is a rare cause of IR. Patients who have a combination of hyperglycemia, IR, AN, and autoimmune features can have insulin receptor antibodies. These patients improve with glucocorticoid therapy. (32).
IGF-1 and AN

High circulating concentrations of IGF-1 are associated with a reduced risk of developing impaired glucose tolerance and type II diabetes mellitus in individuals with normal fasting glucose levels. In people with low levels of IGF-binding protein 1 (IGFBP-1), the IGF-1 concentration is high (33-35). Insulin suppresses the production of IGFBP-1, increases the sensitivity of the growth hormone (GH) (also known as Somatomedin) receptors, and enhances the biological activity of GH in the liver. (36, 37).

Insulin is the main positive regulator of Hepatic IGF-1 production and hyperinsulinemia increases circulating IGF-1 levels. The circulating concentration of IGFBP-1 is controlled by insulin and the raised biologically active fraction of IGF-1; which induce tissue modifications in obese subjects with insulin resistance. AN in Insulin Resistance could thus be secondary to increased binding of the active fraction of IGF-1 to both keratinocyte IGFR and insulin receptors. In addition, insulin resistance is increased at puberty (38) and seems related to fat accumulation (30). As a result, AN is usually more frequent in adolescents.

Elevated insulin concentrations result in direct and indirect activation of IGF-1 (IGF = insulin-like growth factor 1) receptors on keratinocytes and fibroblasts, leading to proliferation. Other mediators include: tyrosine kinase receptors such as EGFR and FGFR. (EGFR = epidermal growth factor receptor, FGFR = fibroblast growth factor receptor).

Acanthosis nigricans is most commonly associated with disorders associated with insulin resistance and in these cases, hyperinsulinemia is key to the development of AN (17). Normally insulin binds to "classic" insulin receptors (15). In hyperinsulinemic states, insulin
can exert more potent growth-promoting effects through binding to IGF-1R. Insulin can promote AN through direct activation of the IGF-1 signalling pathway.

Hyperinsulinemia facilitates the development of AN indirectly by increasing the levels of free IGF-1(also known as Somatomedin) in the circulation. Insulin-like growth factor 1 & 2 binding protein is decreased in hyperinsulinemic, obese patients. Insulin-like growth factor 1 is expressed within the stratum granulosum and by dermal fibroblasts, but not by epidermal basal keratinocytes and they bind to receptors with more affinity than Insulin itself.

IGF receptors facilitate the development of AN. Insulin can cross the dermoepidermal junction, and stimulate growth and replication of fibroblasts. The severity of AN in obesity correlates positively with the fasting insulin concentration. Obese patients rarely achieve high levels of insulin. Constant friction, sweating and rubbing of the area to get rid of the pigmentation may be co-factors in the development of AN in the flexural areas (18, 39).

Insulin-like growth factor 1 may reduce serum insulin concentrations and down regulate expression of IGF-1R ((40). Insulin may be less proficient than IGF-1 at down regulating IGF-1Rs. No insulin resistance is described for most cases of para neoplastic AN (14). Malignancy-associated AN might be explained by elevated levels of growth factors such as transforming growth factor (TGF-α), which exerts effects through the EGFR (41). AN syndromes can also be due to FGFR defects.

AN cannot be dismissed by the clinician as a mere skin change. Components of the metabolic syndrome: obesity, hypertension, elevated triglycerides, low high-density lipoprotein, and glucose intolerance have to be watched out for. The metabolic syndrome, yields a risk of heart disease equivalent to smoking and in adults increases the risk of the development of diabetes. PCOS is associated with insulin resistance, hyperinsulinemia, and AN with increased
synthesis of ovarian and adrenal androgens and inhibition of synthesis of sex hormone-binding globulin. For the dermatologist Insulin resistance is also a culprit for the development of acne, skin tags, male pattern balding, myopia, and epithelial cell cancers.

Obesity has become a very common diagnosis today and is reported in the etiology of a number of diseases. Talking to the patient and their immediate family helps develop a better support group and simultaneously treats obesity. Non-pharmacologic lifestyle modifications with diet and exercise can be initiated. For those presenting with hypertension and elevated fasting lipid profiles medications may become necessary if not brought within control. Improvement of the skin lesions is often the patient's primary concern. Multiple case reports suggest that AN improves with treatment of its underlying condition. A brief diagrammatic representation of the pathogenesis of AN is given in fig 1.3.
1.1.3. CLASSIFICATION OF ACANTHOSIS NIGRICANS

The classification of AN according to Schwartz was published in 1994 (9).

TABLE 1.1: CLASSIFICATION OF ACANTHOSIS NIGRICANS (AN)

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Benign Familial AN</td>
<td>Autosomal dominant inheritance, with variable penetrance, increasing till puberty and then stabilizing.</td>
</tr>
<tr>
<td>Pseudo AN (obesity associated)</td>
<td>This usually moderate variant is clearly related to obesity, regressing when obesity regresses. It is the most frequent type of AN and thus the term Acanthosis nigricans vulgaris would be appropriate. Obese patients rarely achieve high levels of insulin.</td>
</tr>
<tr>
<td>Syndromic AN</td>
<td>Type A affecting young women with signs of virilization or accelerated growth. Type B autoimmune due to autoantibodies directed against the insulin receptors. Besides these variants there are other numerous syndromes, like: Hirschowitz syndrome, familial, characterized by early onset, deafness and gastrointestinal disorders and Lawrence-Seip syndrome with associated lipodystrophy.</td>
</tr>
<tr>
<td>Malignant AN</td>
<td>It is characterized by sudden onset and it is sometimes associated with other cutaneous markers of malignancy such as eruptive seborrheic warts (Lesser-Trelat Sign), florid cutaneous papillomatosis and hyperkeratosis of the palms and soles. The onset is aggressive and frequently involves the Oral mucosa, Palms and Soles. Unintentional weight loss and rapid onset of extensive AN, necessitate investigations to rule out malignancies. Mucosal involvement, tripe palms, florid cutaneous papillomatosis, and the Leser-Trélat sign are more common in patients who have AN in association with a malignancy.</td>
</tr>
<tr>
<td>Acral AN</td>
<td>Seen on the dorsal aspect of the hands and feet, which is almost physiological in dark-skinned subjects. It is also named acralacanthotic anomaly.</td>
</tr>
<tr>
<td>Unilateral or nevoid</td>
<td>It can be the initial sign of the benign familial variant and then progress to bilateral or may persist as monolateral involvement.</td>
</tr>
<tr>
<td>Drug induced</td>
<td>Steroid hormones, Lipid lowering agents, Nicotinic acid and Topical Fusidic acid.</td>
</tr>
<tr>
<td>Mixed</td>
<td>Characterized by the simultaneous presence of two associated variants of AN</td>
</tr>
</tbody>
</table>

Source: Adapted from Schwartz, 1994
1.1.4. TREATMENT OPTIONS FOR AN

A randomized, open-label trial that compared the insulin sensitizers Metformin and Rosiglitazone in 30 overweight Mexican patients for 12 weeks demonstrated only minimal improvement in AN lesions with either agent (42). The weakness of the study was the short duration of therapy. A smaller, 6-month trial of metformin in obese patients resulted in improvement of AN in 3 of 5 patients (43).

Retinoids have been successfully used to treat AN. Topical 0.1 percent tretinoin caused improvement of AN in two case reports (44). The combination of 0.05 percent tretinoin cream and 12 percent ammonium lactate cream led to resolution of AN (45).

Acanthosis Nigricans is reversible. Although therapeutic interventions are being employed with reasonable results, such as retinoids; their superiority over other medications remains unclear. Very few randomized, controlled trials exist for any treatment of AN to our knowledge. Randomized, controlled trials of lifestyle intervention and other therapies are needed (46).

1.1.5. GRADING

Burke et al., developed and validated a scale for AN grading applicable to the Mexican American population. The neck, axilla, elbows, knuckles, and knees were examined. Except the neck, all other locations were excluded from further analyses. AN neck, as per their study correlated well with fasting insulin and BMI (47). But Kobaissi et al., in a previous study declared that AN grading for texture and severity were not useful in determining the severity
of insulin resistance (16). The grading took into account the extent and the texture of the AN as in Fig 1.1.

1.1.6. AN OF THE VULVA

A cross-sectional observational study was conducted among women of reproductive age. They were non-hypertensive, non-diabetic with hyperandrogenism, without medications known to influence lipid, carbohydrate, or hormonal metabolism. IR was assessed. AN was identified at several body sites. It was always present on the vulva in women who displayed one or more lesions. Acanthosis nigricans was found only in the obese, hirsute, hyperandrogenic women. These women were the most insulin resistant. The vulva is one of the most likely places to find this marker (48).

1.2. PRE DIABETES

Pre diabetes is the intermittent period between normal glucose tolerance and diabetes mellitus. Progression from normal glucose tolerance to overt type 2 diabetes in adults involves an intermediate stage of impaired glucose tolerance, referred to as prediabetes (49).

In obese children and adolescents with prediabetes, intra myocellular and intra-abdominal lipid accumulation is closely linked to the development of severe peripheral insulin resistance (50).

Pre-diabetes was diagnosed if the fasting plasma glucose was $\geq 110$ (≥ 6.1 mmol/l) and $<126$ mg/dl (<7 mmol/l), impaired fasting glycemia (IFG) or 2 hour post glucose was $\geq 140$ mg/dl ($\geq 7.8$ mmol/l) and $<200$ mg/dl (<11.1 mmol/l) – impaired glucose tolerance (IGT) (51). The
CUPS (Chennai urban population study) study showed that the incidence of pre-diabetes is very high (13.1%) among urban south Indians.

Prediabetes is linked to relative insulin deficiency and tissue insulin resistance causing abnormal blood glucose levels despite secondary hyper-insulinaemia. IFG is associated with hepatic insulin resistance, resulting in fasting hyperglycaemia, and IGT is associated predominantly with skeletal muscle insulin resistance (52).

In 2002, the American Diabetes Association and the United States Department of Health and Human Services defined prediabetes as the condition in which blood glucose levels are elevated above the normal range but do not satisfy the criteria for the diagnosis of diabetes mellitus, defined by the World Health Organization. For practical purposes, only a single plasma glucose measurement in the defined category, rather than two on separate days, is required to diagnose prediabetes, with testing done in the absence of severe metabolic stress or illness (53).

Prediabetes is also defined as the presence of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) This is consistent with current National Health and Medical Research Council guidelines for screening for diabetes. A single abnormal reading at formal testing is adequate to define prediabetes. People who have prediabetes are at increased risk of developing diabetes, although a proportion of those with prediabetes can revert to normal glucose tolerance. Prediabetes may be incidentally detected when screening for diabetes. There is no current proven clinical role for specifically screening for prediabetes (54).

Many studies conducted prospectively have established the progression of pre diabetes to Diabetes Mellitus (55, 56). Subjects with both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have a six times higher risk of acquiring DM in the future than either
alone (54). IGT is more sensitive (57) and IFG is more specific (58) in predicting the development of DM in future.

1.2.1. INDIAN SCENARIO

A recent cross sectional survey published in 2012 found that among participants enrolled from eight India states, 18.4% were classified as having prediabetes and 60.1% as having prehypertension. Diabetes was prevalent in 34.7% patients, and 46.0% of the subjects had hypertension. Diabetes and hypertension were coexistent in 20.6% patients. At enrollment, 7.2% subjects were newly diagnosed with diabetes and 22.2% subjects were newly diagnosed with hypertension. A positive association ($P<0.05$) was observed between diabetes/hypertension and age, familial history of either, a medical history of cardiovascular disorders, alcohol consumption, and diet (59)

1.3. INSULIN RESISTANCE

IR can broadly be divided into two syndromes. Type A, a syndrome in younger females with signs of virilization or accelerated growth, in whom the receptor defect may be primary, and Type B, a syndrome in older females with signs of an immunologic disease, in whom circulating antibodies to the insulin receptor are found. When IR subjects were fasted, there
was a fall in plasma insulin but no increase in insulin binding. Thus the receptor defect was not secondary to the hyperinsulinemia (6).

Insulin resistance in the pre-diabetic state is associated with the presence of additional cardiovascular risk factors. Chronic sub-clinical inflammation measured by inflammatory markers such as C-reactive protein (CRP) is associated with IR and other features of the insulin resistance syndrome, increased risk of development of type 2 diabetes and increased cardiovascular event risk. (60).

A recent study in Spain compared IR and MetS among 292 non diabetic adults. A diagnosis of IR was made when fasting plasma glucose was more than 110mg/dl.

1.3.1. INSULIN RESISTANCE AND ACANTHOSIS NIGRICANS

Acanthosis Nigricans (AN) has been proposed as a reliable marker of hyperinsulinemia, in obese children. Insulin resistance is the hallmark of the pathophysiology of type 2 diabetes mellitus. Subjects with hyperinsulinemia and impaired glucose tolerance are well accepted as being at high risk for diabetes. Childhood benign Acanthosis nigricans is tightly associated with obesity, hyperinsulinemia, insulin resistance and type 2 diabetes mellitus, and may be used as a reliable index of insulin resistance (61).

Many endocrine disorders manifest themselves as skin afflictions. Insulin Resistance (IR) is a continuously high level of plasma insulin in response to a glucose challenge due to a resistance to insulin at a cellular level (62). It can affect any age, gender or race and is a precursor to obesity, vascular disorders, infertility, growth abnormalities, cardiac complications and type II DM (63). IR is reversible by lifestyle modification (64). A recent study showed that IR was never present in patients without AN (23).
Insulin and insulin-like growth factor-1 (IGF-1), and their receptors on keratinocytes are involved in the complex regulations leading to the peculiar epidermal hyperplasia (65). Dark, rough skin on the back of the neck is Acanthosis Nigricans (AN). A scale for the quantitative analysis of AN was put forward by Burke et al., (47) and Stuart proposed the correlation between the presence of AN and IR (66).

1.3.2. INSULIN RESISTANCE AND HIRSUTISM

Adolescent girls with Polycystic Ovarian Syndrome and IR are more hirsute. They have higher grades of AN, lower Sex Hormone Binding Globulin (SHBG) and higher fasting insulin levels compared to non-insulin resistant girls (67). Hirsutism was associated with a greater incidence of insulin resistance, with an increase of 17-hydroxyprogesterone, ovarian and adrenal androgens, 3alpha-androstanediol glucuronide, insulin, insulin-like growth factor-I and low luteinizing hormone, sex hormone binding globulins and insulin-like growth factor binding protein-1 levels (68).

1.3.3. ACANTHOSIS NIGRICANS AND OTHER DERMATOSES

AN associated with many different systemic diseases, endocrine disorders and internal malignant neoplasms have been described. The association of AN with severe atopic dermatitis (AD) and Down’s syndrome was described in 2001. An 82 month retrospective study was conducted on 1038 patients. AN was more frequent in patients with severe AD and in 100% of cases of hand dermatitis and juvenile plantar dermatosis, located on the interphalangeal and metacarpophalangeal joints, whereas in Down syndrome other flexures were also affected. The pathogenesis of AN in AD is unknown, but in Down syndrome it seems to be related to obesity. (69).
AN, insulin receptor antibody, and systemic lupus erythematosus (SLE) are associated in the lethal syndrome of type B insulin resistance. Hyperpigmentation is rare, while glucose intolerance is common. IR may be mild or transient in some patients with type B insulin resistance. Resolution of skin lesions was noted during therapy of SLE, and was associated with disappearance of insulin receptor antibody (70).

1.3.4. DIAGNOSING TECHNIQUES FOR IR

The OGTT was originally developed to classify carbohydrate tolerance but has also been used to evaluate β-cell function and insulin resistance (71). Fasting plasma insulin concentrations have been used as an index of insulin resistance (72).

Hyperglycemic and euglycemic hyperinsulinemic clamp studies are well established for assessing -cell function and insulin sensitivity, but impractical for population based screening (73). Stumvoll et al., in their study of 104 non diabetic people, compared plasma glucose and insulin responses during the OGTT with hyper-glycaemic and euglycemic-hyperinsulinemic clamp procedures and found them to be equally effective. They thus advocate the OGTT as an ideal screening tool for insulin resistance (71).

There is no role for routine home capillary blood glucose monitoring or glycated haemoglobin (HbA1c) in monitoring prediabetes.

1.3.5. IR AND RAISED LIPIDS

Diabetes mellitus is commonly associated with hypertension, and the link is hyperinsulinemia. A heightened plasma insulin response to a glucose challenge is consistent. The insulin resistance of essential hypertension is located in peripheral tissues (muscle) and is limited to nonoxidative pathways of glucose disposal (glycogen synthesis), and correlates directly with the severity of hypertension.
The reasons for the association of insulin resistance and essential hypertension can be sought in at least four general types of mechanisms:

- Sodium retention.
- Sympathetic nervous system overactivity.
- Disturbed membrane ion transport.
- Proliferation of vascular smooth muscle cells.

Calorie restriction in the overweight and regular physical exercise, can improve tissue sensitivity to insulin. Insulin resistance and hyperinsulinemia are associated with an atherogenic plasma lipid profile.

Hyperinsulinemia enhances very-low-density lipoprotein (VLDL) synthesis. Progressive elimination of lipid and apolipoproteins from the VLDL causes an increased formation of intermediate-density (IDL) and low-density lipoproteins (LDL), both of which are atherogenic.

Insulin, is also atherogenic. It enhances cholesterol transport into arteriolar smooth muscle cells, increases endogenous lipid synthesis, stimulates the proliferation of arteriolar smooth muscle cells, augments collagen synthesis in the vascular wall, increases the formation of and decreases the regression of lipid plaques, and stimulates the production of various growth factors. (74).

1.3.6. IR AND DIET

Dietary glycemic load may be one environmental factor contributing to the variation in acne prevalence worldwide. Studies have been conducted to study the effect of a low glycemic load diet on the endocrine aspects of acne vulgaris. At the end of the study period, Smith R et al noted changes in the homeostasis model assessment of insulin resistance (HOMA-IR), sex
hormone binding globulin (SHBG), free androgen index (FAI), insulin-like growth factor-I (IGF-I), and its binding proteins (IGFBP-I and IGFBP-3). Changes in HOMA-IR were significant. This suggests that increases in dietary glycemic load may augment the biological activity of sex hormones and IGF-I, suggesting that these diets may aggravate potential factors involved in development of the skin changes associated with IR (75).

1.3.7. CARDIOVASCULAR DISEASE RISK

Prediabetes is associated with an increased risk of developing cardiovascular disease (76) more so in younger adults (77). Some studies indicate that people with IGT and normal levels of fasting plasma glucose have a greater risk of CVD than those with IFG (78). An increasing IGT is associated with a greater risk of cardiovascular death (79). Twigg et al., proposed that pre diabetes is a continuum of “Cardio-metabolic risk”. Children with AN had a higher chance of having a raised blood pressure especially when overweight (80).

1.3.8. BURDEN OF IR

A recent study conducted in 6 different cities support the prevalence rate, which shows very high prevalence in Chennai (13.5%), Bangalore (12.4%), Hyderabad (16.6%), Mumbai (9.3%), Delhi (11.6%) and Kolkata (11.7%) (81). Prediabetes prevalence is 16.4% in Australian adults aged 25 years or more (82).

1.3.9. SKIN CHANGES OF IR

Fasting levels of Serum Insulin secreted by the Islets of Langerhans, when raised are highly suggestive of IR (83). There is a noticeable increase in the prevalence of IR among the overweight and obese population (84). The other skin changes of IR include Acrochordons, hirsutism, striae distensae, acne vulgaris and male pattern baldness.
1.3.10. ACROCHORDONS (SKIN TAGS) AND IR

Jowkar et al., found that the insulin level in subjects with acrochordons was significantly higher in the cases compared to controls in their case control study. They also concluded that insulin plays a significant role in the pathogenesis of skin tags and that the role of IGF-1 in the same is questionable, though implicated (85).

At the therapeutic level, a randomized trial showed that the use of the oral hypoglycemic drug in patients with AN resulted in a significant decrease in insulin level but this was not associated with a significant clinical improvement.

Although previous studies have discarded AN grading as ‘not very useful’ in determining the severity of IR, our study proved otherwise (16). Skin tags or acrochordons are small flesh coloured to dark brown sessile or pedunculated papillomas that commonly occur in flexures. They are commonly associated with Diabetes mellitus (86) and obesity (87). High levels of circulation insulin, in insulin resistance as well as glucose can induce fibrogenesis in the skin, insulin being a well established growth promoting hormone (26).

Rodriguez et al., in their recent publication concluded that AN and acrochordons when presents in children who are of healthy weight or overweight are indicators of an underlying IR (88).

1.4 LIFESTYLE MODIFICATIONS

Increased body weight and sedentary behaviour accelerate IR and β-cell dysfunction, leading to the clinical manifestations of hyperglycaemia. The primary steps in the control of type 2 diabetes remain long-term behavioural changes for patients and society as a whole (89).

Many randomised studies have evaluated the benefits of lifestyle interventions in pre diabetes. The Diabetes Prevention Program(DPP) recommended a weight loss of 7% from total body
weight and 150 minutes of moderate physical activity every week to reduce the risk of progression to DM (90).

Both the DPP and the Finnish Diabetes Prevention Study recorded a 58% relative risk reduction in the progression to DM with Lifestyle modification (LSM) (91). Change in the quality of food i.e. fat intake < 30% of total energy intake; saturated fat intake < 10% of total energy intake; dietary fibre intake ≥ 15 g/1000 kcal; and at least moderate intensity exercise for > 240 minutes every week showed lowest diabetes development (56).

Pan et al., studied the benefits if LSM and diet, alone and in combination, in the management of Pre diabetes and found that the exercise arms had the higher reductions in the relative risk of development of DM (55). Other clinical trials, one in Japan showed a relative reduction in development of diabetes of 67% (92) and one in South India showed a relative risk reduction of 29% with lifestyle modification, similar to that in a parallel group treated with both metformin and lifestyle intervention (93). Diet and exercise, as lifestyle modification have been recommended for a minimum period of 6 months before initiating pharmacotherapy in the DPP (90).

Hamdy et al concluded that 6 months of consistent weight reduction and exercise improved macrovascular endothelial function and reduced selective markers of endothelial activation and coagulation in obese subjects with IR regardless of the degree of glucose tolerance (64).

1.5. METFORMIN – PHARMACOTHERAPY

Many randomized, double-blinded, prospective trials, aimed to study the impact of medication in lowering the conversion of prediabetes into full blown diabetes mellitus. They
have studied a variety of oral hypo-glycaemic agents. The DPP included 850 mg of metformin, twice daily and showed a 31% risk reduction in the progression to diabetes (90) which was maintained on stopping the medication in 83% of the subjects. The STOP-NIDDM trial, used the glucosidase inhibitor acarbose, 100 mg three times daily and noticed a reduced progression to diabetes by about 25% after 3.3 years (94). The TRIPOD study, used Troglitazone in women with a history of gestational diabetes. The DREAM study used rosiglitazone, 8 mg daily for 3 years, and recorded a reduced the risk of diabetes or death by 60% in and the XENDOS study used the gastrointestinal lipase inhibitor orlistat three times daily and noticed a reduced diabetes risk by 37% over 4 years in obese adults with prediabetes (95-97).

Insulin-sensitizing agents may have greater effects in reducing cardiovascular risk than secretagogues in the pre-diabetic state, and glitazones have been found to decrease CRP levels in patients with diabetes. Statins also reduce CRP levels. Efforts to reduce CVD should include increased emphasis on improving glycaemic control, preventing development of diabetes and addressing cardiovascular risk factors in the pre-diabetic state (60).

IGF-1-lowering agents (such as tamoxifen, fenretinine and octreotide) may help in the management of AN (associated with polycystic ovary) and in the prevention of the recurrence of acrochordons after surgical removal (98).

There is a strong relationship between excess weight and type 2 diabetes. Hence, weight control and lifestyle modificationss contribute largely to the success of any specific treatment. (8, 99). Exercise promotes insulin uptake and utilisation and hence lowers fasting insulin levels. Increasing the physical activity while dieting for prolonged periods is difficult, especially for adolescents and children (90, 100). Attention distraction like music, in the physical activity or group activities and outdoor sports help break the monotony of physical
exercise (101). Somatostatin is beneficial in the management of AN, especially when given long term.

It reduces insulin secretion in hyperinsulinemia and severe obesity with reduction in insulin binding to IGFR. Long-term treatment with Octreotide, a synthetic analog of Somatostatin has shown improvement in the grades of AN (102). Colecalciferol, a Vitamin D analog; increases keratinocyte differentiation while inhibiting their proliferation (103). Topical calcipotriene ointment may be an effective treatment, as it reduces the hyperkeratotic and papillomatous skin changes. Oral retinoids may also be of some benefit in these patients (104) But they are effective only when hyperinsulinemia is controlled. (8, 29).

AN management can involve both increasing the insulin sensitivity and reducing the hyperinsulinemia. Metformin, a biguanide drug, usually used in type 2 diabetes, suppresses endogenous glucose production by increasing both the peripheral response to insulin and the cellular glucose metabolism (105). It acts by potentiating phosphatidylinositol-3' kinase pathway of insulin receptors. (31). Liver glucogenesis and intestinal absorption of glucose are delayed. Androgen levels are reduced and SHBG concentrations are increased (106, 107). Treatment with metformin causes transient abdominal discomfort and diarrhoea in some patients (108).

Acarbose, an α-glucosidase inhibitor, reduces postprandial hyperglycemia. In the course of time insulin sensitivity improves (109). Thiazolidinediones, increase skeletal muscle insulin sensitivity, the major site of insulin resistance. Eg. Rosiglitazone and Pioglitazone (38). It can be used in combination with metformin.

One study showed that a combination of Cyproterone acetate (CA) and Ethinyloestradiol (EO) used as anti-androgen therapy for the treatment of hirsutism and/or acne, could reduce
fasting plasma glucose and raised fasting plasma insulin concentrations, causing insulin resistance. Hyperinsulinaemia was due to a reduction of hepatic uptake of insulin rather than its increased secretion. EO alone, showed impairment of glucose tolerance with no change in insulin levels. (110).

1.6. CHILDREN AND AN

Children and adolescents with T2DM had a significant family history of DM and clinical features of insulin resistance, including increased body mass index, waist:hip ratio and Acanthosis Nigricans. They also had decreased insulin sensitivity together with dyslipidemia of metabolic syndrome, i.e. high triglyceride, high total cholesterol and low HDL-cholesterol. The presence of these predictors of cardiovascular disorders is known to contribute to morbidity and mortality. Hence, DM II needs to be recognized early in Asian Indian children. (111)

A relationship exists between the AN, obesity, and elevated blood pressure in school-age children (2).

1.7. TYPE II DM IN CHILDREN

Children and adolescents with T2DM had a significant family history of DM and clinical features of insulin resistance, including increased body mass index, waist:hip ratio and Acanthosis Nigricans. They also had decreased insulin sensitivity together with dyslipidemia of metabolic syndrome, i.e. high triglyceride, high total cholesterol and low HDL-cholesterol. The presence of these predictors of cardiovascular disorders is known to contribute to morbidity and mortality. Hence, DM II needs to be recognized early in Asian Indian children. ((111).
Juvenile onset diabetes is characterized by acute onset, absence of Acanthosis Nigricans (AN) lesions and is more frequently observed in children who are <75th percentile for BMI at diagnosis. However, type 2 diabetes or adult onset diabetes, characterized by a more asymptomatic onset and a BMI of > 85th percentile, is often associated with AN lesions at diagnosis (112).

IR starts in childhood, following pediatric and adolescent obesity together with low physical activity (113). Type 2 diabetes occurs when the body develops a resistance to endogenous insulin or no longer uses its own insulin properly. Eventually the pancreas loses its ability to produce sufficient quantities of insulin and overcome the resistance and regulate blood glucose. Hypertension, and dyslipidemia often accompany IR.

AN can be classified as follows (9) Benign AN, Pseudo AN associated with obesity, Syndromic AN, Malignant AN, Acral AN, Unilateral AN, Drug-induced AN and Mixed AN. In IR the back of the neck is the region most commonly involved with AN as shown in table 1.1. The axilla is almost as frequently involved. AN doesn't cause any symptoms other than skin changes. Clinically, the neck is the most easily accessible area for AN. Skin colour may influence the presence of AN. Taking into consideration Phototypes I-VI of Fitzpatrick, people with skin phototype IV have a high frequency of AN on the neck (19).

The β cells of the pancreas secrete insulin which bind to their receptors on plasma membranes and enter the cell. Insulin resistance is of three types (i) Pre – receptor : due to anti bodies to insulin, (ii) Receptor : due to reduced number of receptors and (iii) Post receptor : due to abnormal signal transduction or reduced sensitivity of the peripheral tissues to insulin; as in obesity (114).
This excess plasma insulin binds to insulin like growth factors which are normally present in the skin and cause proliferations of keratinocytes and fibroblasts seen in AN. It also causes hyper-androgenemia in post pubertal females, by stimulating the ovarian production of androgens in the presence of LH (115).

Being overweight promotes insulin resistance rather than results from it (116).
Factors influencing the development of Acanthosis Nigricans

Obesity
  ↓
Insulin Resistance
  ↓
Hyperinsulinemia
  ↓
↑ TGF
  ↓
↑ IGF -1
  ↓
Activation of IGF-1R
  ↓
FR, FGFR  AN  Other Factors

TGF – transforming growth factor
IGF 1 – Insulin like growth factor 1
IGF 1R – Insulin like growth factor 1 receptor
1.8. MANAGEMENT

Metformin and other insulin sensitizing drugs are approved for the management of IR. But these are not without complications. Keeping this in mind, lifestyle modification is considered as an alternative mode of treatment. Weight loss reverses the insulin resistance and compensatory rise in insulin levels. Metformin, octreotide, retinoids and topical colecalciferol have helped clear AN (65).

TABLE 1.2: STUDIES COMPARING LIFESTYLE MODIFICATION AND PHARMACOTHERAPY IN MANAGING DIABETES MELLITUS

<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>Target for intervention</th>
<th>Relative risk reduction in progress to DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Diabetes Prevention Program (117)</td>
<td>Katula JA et al.,</td>
<td>7% wt loss &amp; moderate activity 150min/week</td>
<td>58%</td>
</tr>
<tr>
<td>The Finnish Diabetes Prevention Study (91)</td>
<td>Tuomilehto J et al.,</td>
<td>wt loss &gt; 5%; fat &lt; 30% of total energy intake; saturated fat &lt; 10% of total energy intake; dietary fibre intake 15 g/1000 kcal; moderate intensity exercise for &gt; 4 hours weekly</td>
<td>58%</td>
</tr>
<tr>
<td>Da Qing IGT and Diabetes Study (118)</td>
<td>Pan XR et al.,</td>
<td>diet alone</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exercise alone</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diet plus exercise</td>
<td>42%</td>
</tr>
</tbody>
</table>
Though consistent lifestyle modifications are proven to bring about loss of body weight in people with pre-diabetes, the benefits of reducing fat and carbohydrate intake cannot be overestimated over the benefits of regular exercise (54).

TABLE 1.3: PHARMACO-THERAPEUTIC TRIALS IN INSULIN RESISTANCE (54)

<table>
<thead>
<tr>
<th>TRIAL NAME</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP-NIDDM</td>
<td>Glucosidase inhibitor – acarbose.</td>
</tr>
<tr>
<td></td>
<td>100 mg three times daily</td>
</tr>
<tr>
<td>TRIPOD (gestational DM)</td>
<td>Troglitazone</td>
</tr>
<tr>
<td>DREAM</td>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>XENDOS (Obese + Pre diabetes)</td>
<td>Orlistat</td>
</tr>
</tbody>
</table>

Diet and exercise as part of lifestyle modification should be given preference over medical intervention in the pre diabetic population. Withholding metformin for 6 months during which time the subjects are put through monitored lifestyle changes and weight loss has been recommended in the Diabetes Prevention Program. Failure of lifestyle modification would include weight gain rather than weight loss and no evidence of increased physical activity or achievement of recommended macronutrient dietary change (54).
1.9 IR & ACNE

Acne is associated with the lowest 3 alpha-androstenediolglucuronide levels. Two different pathogenetic mechanisms may play a role in the onset of acne and hirsutism (68). A study was conducted to evaluate serum levels of basal insulin and glucose-stimulated insulin, and to evaluate their correlations with androgen levels in women with acne. Serum levels of total testosterone (T), free testosterone (FT), dihydrotestosterone (DHT), dehydroepiandrosteronesulfate (DHEA-S), sex hormone binding globulin (SHBG), insulin-like growth factor-1 (IGF-1), and immunoreactive insulin (IRI) were measured. Serum FT, DHT and DHEA-S levels in the acne group were significantly higher in the control group. In the acne group, there were no significant correlations between insulin or IGF-1 levels and FT, DHT and SHBG, despite the positive correlation between insulin and IGF-1. Examination of the responses of serum insulin and androgen levels to a 75 g, 2 hour OGTT showed Basal insulin levels were not significantly higher than those in the control group, but the summed insulin levels during the OGTT in the acne group were significantly higher than those in the control group. There is mild insulin resistance during the OGTT in acne patients. However, postmeal transient hyperinsulinemia does not seem to play an important role in determining hyperandrogenemia in acne patients (120).

1.10 IR & PCOS

Androgenetic disorders in women are frustrating and present with persistent acne, hirsutism and androgenic alopecia, which is the female equivalent of male pattern baldness. A subgroup of those women, traditionally labelled as having polycystic ovary syndrome (PCOS), additionally have anovulation, as well as menstrual abnormalities and, often, obesity. The Gynaecologist or the Dermatologist is their first consult for menstrual or skin changes. Women with PCOS have varying degrees of insulin resistance, an increased incidence of
Type II diabetes mellitus, as well as unfavourable lipid patterns, suggested by upper segment obesity, darkening of the skin, and the other skin changes that make up Acanthosis nigricans. Diagnosis involves measurement of free testosterone, prolactin and FSH when menstrual dysfunction is present. Many women with androgenic skin changes have normal serum androgen levels, suggesting increased end organ sensitivity to androgens. Others have hyperandrogenism (of ovarian or adrenal origin). Treatment to suppress androgen levels, is usually successful in controlling acne, reducing hirsutism and stabilizing, or partially reversing, androgenic alopecia (121).

Mutations in the insulin receptor genes: 21-hydroxylase, 11 beta-hydroxylase, and 3 beta-hydroxy steroid dehydrogenase isomerase enzymes are associated with hyperandrogenism, causing less than 10% of all cases (39).

The insulin resistance and the consequent hyperinsulinemia are associated with AN in the male, with AN and hyperandrogenemia in the female. Hyperinsulinemia is also responsible for hyperandrogenemia, by stimulating the ovary production of androgens. The latter occurs only in presence of LH and thus it occurs only in females after puberty (115).

Women with AN and masculinization, had the findings suggestive of polycystic ovarian disease. All AN subjects had significant IR. Anovulation, sclerosis of the ovarian cortex, follicle cysts, and stromal hyperthecosis were consistently reported (122).

In a study of 81 overweight-obese women with PCOS (diagnosed as per the Rotterdam 2003 criteria) BMI, abdominal circumference, hirsutism, acne and AN were noted. Serum testosterone, sex hormone binding globulin, fasting plasma glucose and insulin levels were measured. There were no differences in age, frequency of hirsutism, acne, serum testosterone and fasting glucose levels between insulin-resistant and insulin-sensitive women. However,
there were significant differences in BMI, Abdominal Circumference, frequency of AN, SHBG levels and fasting insulin levels between the two groups. PCOS women with IR are thus more obese; they have more upper body adiposity and AN. They are more hyperandrogenic. Simple clinical parameters will help to suspect IR in PCOS women (67).

1.11 IR & PREGNANCY

The new onset non-proteinuric hypertension of late pregnancy is associated with a high risk of essential hypertension later and glucose intolerance. These conditions may thus have a similar pathophysiology. To assess this association and the subsequent development of proteinuric and non-proteinuric hypertension in pregnancy in women without underlying essential hypertension, a study was conducted which included only pregnant women. Glucose (fasting, 1 and 2 hours postglucose load), fasting serum insulin, glycosylated hemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL-C), and triglycerides levels were documented. Women who developed hypertension in pregnancy, had higher glycemic levels (fasting, 1 and 2 hours postglucose load) on a 100-gram oral glucose loading test, although only the fasting values showed a statistical significance (123). Gestational diabetes mellitus (GDM) reverts to normal post-delivery, leaving behind an increased risk of T2DM. Gut glucose absorption rates were <=52% lower from 30 to 120 min (P<0.03 vs. conditions after delivery or NGTpreg). In Gestational DM, OGTT gut glucose absorption is markedly lower during hyperglycemia (124).

1.11.1 DIAGNOSIS of AN

Diagnosis of AN is usually clinical, supported by histological examination. Microscopic AN was found in people with DM and normal population wherein skin biopsy was done. Fasting insulin levels most strongly predicted the presence of AN in normal population (125).
1.11.2 LABORATORY FINDINGS

The OGTT is a good indicator of the Impaired Glucose Tolerant status of the subject. Blood glucose levels at fasting and after glucose load are evaluated every 30 minutes up to 2 hours (126). Insulin resistance is diagnosed when the two hour glucose challenge value falls between 140 and 200 mg/dl. Investigations for hyperandrogen state and Cushing disease is necessary and includes determinations of serum levels of total testosterone, dehydroepiandrosteronesulfate (DHEA-S) and gonadotropin concentrations, as well as 24-hour urinary cortisol levels.

Pelvic ultrasonography is performed for confirming a possible polycystic ovary syndrome.

1.12 ALERTING FACTORS FOR IR

There is an association between waist circumference (WC) and IR. Waist circumference is a predictor of insulin resistance syndrome in children and adolescents and could be included in clinical practice as a simple tool to help identify the population at risk (127).

1.13 IR & OTHER COMORBIDITIES

The patients with AN, who are euglycaemic with hyperinsulinaemia have a cluster of risk factors for cardiovascular disease (128). Thyroid dysfunction should be sought in these subjects as it is commonly associated with IR and can be easily treated (129).

Acrochordons are skin markers in Insulin resistance, and have a higher prevalence of Ultrasound-detected thyroid nodules and larger thyroid glands. Then, it may be beneficial to search for thyroid abnormalities in those subjects with skin tags or IR (130).
1.14 IR & HYPERTENSION

Insulin cannot cause relaxation of vascular smooth muscles or transport glucose to the skeletal muscle tissue. Angiotensin II, inhibits the actions of Insulin by inhibiting phatidylinositol 3-kinase (PI3K) probably by oxidative stress. Hence inhibition of this signalling results in decreased endothelial cell production of nitric oxide, increased myosin light chain activation with vasoconstriction, and reduced skeletal muscle glucose transport. Persons with essential hypertension, thus have a higher risk of developing diabetes (131).

Some common anti hypertensives and their effect on the development of Type 2 DM.

Drugs that increase the risk :
B blockers, Diuretics.

Drugs that decrease the risk :
ACE inhibitors, Angiotensin II receptor blockers

Drugs that have no effect :
Calcium channel blockers (132).

1.15. NUTRITION

A number of research projects have been dedicated to understanding the influence of the quality of food on human behaviour. The genetically depressed rat model, the Flinders Sensitive and Resistant Line (FSL/FRL) rats were fed high-fat diets (HFD). This exacerbated their depressive behaviour, impaired their object recognition memory and also increased insulin levels during an oral glucose tolerance test. This can further lead to an understanding of the relationship between Major depressive disorders and Type II DM mediated by the stress of a HFD (133).
1.16. HEALTH CARE DELIVERY

The team of experts who were involved in the implementation of our trial included dermatologists, physicians, dieticians, nurses and a physical fitness instructors. The Finnish Diabetes Prevention Study and the Diabetes Prevention Program, involved expertise in nutrition, physical activity and behavioural change. Individual and group patient education and coaching was used to implement intensive lifestyle change (56).

1.17. PAEDIATRIC AGE GROUP

A recent study involving 325 pre pubertal Arab children showed that gender differences exist in the correlation of adipocytokines like leptin and adiponectin with serum insulin and HOMA IR. This suggests a link between childhood obesity and early onset of DM (134).

1.18. DIAGNOSIS

Prediabetes is often an incidental finding in people who are undergoing biochemical testing for diabetes. Screening for prediabetes, using a stepped approach of a fasting plasma glucose (FPG) measurement and then, if indicated, a 75 g oral glucose tolerance test (OGTT), is cost-effective compared to a 75 g OGTT as a first-line investigation, especially in community screening (135).

Fasting plasma insulin values and HOMA index were very good indicators of IR. Equally good predictors were Fasting plasma glucose levels $\geq 110$ mg/dl, BMI $\geq 25$kg/m2 and triglycerides $\geq 150$ mg/dl (136).

The OGTT was considered the gold standard in one study and a patient was classified as having Impaired Glucose Tolerance if the 2-hour glucose load value was $\geq 140$ mg/dL and $<200$ mg/dL. T2DM was diagnosed in patients with a 2-hour BG value of $\geq 200$ mg/dL (137).
1.20. MEASURING INSULIN RESISTANCE

Previous studies have evaluated the validity and reliability of homeostasis model assessment-insulin resistance (HOMA-IR) index, its reciprocal (1/HOMA-IR), quantitative insulin sensitivity check index (QUICKI) and McAuley's index in hypertensive diabetic patients. HOMA-IR was the best fit of clamp-derived IS. (138).

ORAL GLUCOSE TOLERANCE TEST (OGTT)

Although hyper-glycaemic and euglycemic hyperinsulinemic clamp studies are the gold standard for measuring insulin sensitivity, it is too expensive, time-consuming, and labour-intensive to be of practical use in an office setting. They are impractical for use outside of specialized research centres (71). Homeostatic measurements (fasting glucose/insulin ratio) [HOMA] value and OGTT represent the easiest office-based assessments of IR. The OGTT provides information about insulin resistance and glucose intolerance. Epidemiological studies, screenings of high-risk populations, and large-scale intervention trials can use the OGTT in evaluating cell function and insulin resistance (139). OGTT is a laboratory based assessment of sugar utilization by the body. Patients are requested to arrive on an empty stomach after overnight fasting of 10 hours. The procedure is first explained and their fasting blood sugar level is noted. After a 75grams glucose load which is administered as a drink in 1liter of water, blood is drawn again at 0, 30, 60, 90, and 120 min for determination of plasma glucose is noted (140).

In the Intravenous glucose tolerance test intravenous loading of glucose for 3 minutes is followed by blood testing for insulin levels. This requires more expertise and hence was not the investigation of choice in our study.
IR was determined by Fasting blood glucose < 126mg/dl (141) and 2 hour glucose load of 140 to 199mg/dl (142).

1.21. DEPRESSION AND TYPE II DM

Depression is a commonly reported co-morbidity in Type II diabetes (143). A meta-analysis of ten controlled studies involving 51,331 people was done to evaluate the prevalence and odds ratio of clinical depression in adults with and without Type II DM. MEDLINE, EMBASE and PSYCINFO databases were used with MeSH terms to identify relevant studies. Clinical depression was significantly higher in patients with Type 2 DM than those without [17.6 vs. 9.8%, OR = 1.6, 95%, confidence interval (CI) 1.2–2.0]. Though the prevalence of depression was higher in females (23.8%), the odds ratio for depression in Type 2 DM was higher in males (OR = 1.9, 95% CI 1.7–2.1) than females (OR = 1.3, 95% CI 1.2–1.4). The main drawback in this was the failure to report confounding factors (143).