INTRODUCTION

Dyslipidemia

Definition

Dyslipidemia is elevation of plasma cholesterol, triglycerides (TGs) and low-denisty lipoprotein,with or without a low high-density lipoprotein level that contributes to the development of atherosclerosis.[1]

Causes and classification

Dyslipidemia is a multifactorial & polygenic disorder resulting from an interaction between an individual's genetic background and multiple environmental factors including behavioural and social risk factors.[2]

According to Fredrickson phenotype, there are primary familial causes of dyslipidemia caused by specific genetic abnormality and secondary (acquired) which results from another underlying disorder that leads to alteration in plasma lipids & lipoprotein metabolism. Also, hyperlipidemia may be idiopathic. [3]

Table (1): Primary (familial) causes [4]

	Synonyms	Defect	Increased lipoproteins	Manifistations	Treatment
Type I (a)	Buerger-Gruetz syndrome	Decreased lipoproteinlipase	Chylomicorons	Abdominal pain (pancreatitis) lipemiaretinalis	Diet control
(b)	Familial apoprotein CII deficiency	Altered Apo C_2	Chylomicorons	Skin xanthomas	Diet control
(c)	-	LPL inhibitor in blood	Chylomicorons	Hepatosplenomegaly	Diet control
Type II (a)	Familial hypercholesterolemia	LDL receptor deficiency	LDL	Xanthelasma Arcus senilis Tendon xanthoma	Bile-acid sequestration Statin Niacin
(b)	Familial hypercholesterolemia	Decreased LDL receptor and increased Apo B	LDL VLDL	-	Statin Niacin Fibrates
Type III	Familial dysbeta-lipoproteinemia	Decreased $ApoE_2$ synthesis	IDL	Plamar xanthomas	Fibrates Statin
Type IV	Familial hypercholesterolemia	Increased VLDL production Decreased VLDL elimination	VLDL	Pancreatitis	Fibrates Statin Niacin
Type V	-	Increased VLDL production Decreased LPL	VLDL chylomicrons	-	Niacin Fibrates

LPL = Lipoprotein lipase , LDL = Low density lipoprotein , VLDL = Very low density lipoprotein , IDL = Intermediate density lipoprotein , apo = apoprotein .

Table (2): Secondary (acquired) causes [4]

Exogenous:	Alcohol, oral contraceptive pills, steroids.
Endocrine and metabolic:	Type I and II diabetes, hypopituitarism, hypothyroidism, pregnancy.
Renal:	Chronic renal failure, uremic syndrome, nephritic syndrome.
Hepatic:	Benign recurrent intrahepatic cholestasis, congenital biliary atresia.
Acute and transient:	Burns, hepatitis.
Others:	• Anorexia nervosa. • Heart transplantation. • Hypercalcemia. • Rheumatoid arthritis. • Tobacco use. • Physical inactivity. • Obesity and weight gain. • Drugs: Beta blocker therapy, antidepressants, oral contraceptive pills. • High poly unsaturated fat diet.

Symptoms and signs:

Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD), stroke, and peripheral arterial disease. High levels of TGs (> 1000 mg/dL) can cause acute pancreatitis. High levels of LDL can cause arcus corneae and tendinous xanthomas at the Achilles, elbow, and knee tendons and over metacarpophalangeal joints. Patients with the homozygous form of familial hypercholesterolemia may have the above findings plus planar or tuberous xanthomas. Planar xanthomas are flat or slightly raised yellowish patches. Tuberous xanthomas are painless, firm nodules typically located over extensor surfaces of joints. Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet.

Severe hypertriglyceridemia (> 2000 mg/dL) can give retinal arteries and veins a creamy white appearance (lipemia retinalis). Extremely high lipid levels also give a lactescent (milky) appearance to blood plasma. Symptoms can include paresthesias, dyspnea, and confusion[4]

Diagnosis and screening:

Dyslipidemia is diagnosed by measuring serum lipids, though it may be suspected in patients with characteristic physical findings. [5]

Routine measurements (lipid profile) include total cholesterol (TC), TGs, HDL, and LDL. TC, TGs, and HDL are measured directly; TC and TG values reflect cholesterol and TGs in all circulating lipoproteins, including chylomicrons, VLDL, IDL, LDL, and HDL.

Testing should be postponed until after resolution of acute illness, because TGs increase and cholesterol levels decrease in inflammatory states.[6]

Lipid measurement should be accompanied by assessment of other cardiovascular risk factors, defined as diabetes mellitus, cigarette use, hypertension, and family history of CAD in a male 1st-degree relative before age 55 or a female 1st-degree relative before age 65.

A definite age after which patients no longer require screening has not been established, but evidence supports screening of patients into their 80s, especially in the presence of atherosclerotic cardiovascular disease. [7]

Indications for screening patients < 20 yr are atherosclerotic risk factors, such as diabetes, hypertension, cigarette smoking, and obesity; premature CAD in a parent, grandparent, or sibling; or a cholesterol level > 240 mg/dL or known dyslipidemia in a parent.

Tests for secondary causes of dyslipidemia—including measurements of fasting glucose, liver enzymes, serum creatinine, thyroid stimulating hormone (TSH), and urinary protein—should be performed in most patients with newly diagnosed dyslipidemia, and when a component of the lipid profile has inexplicably changed for the worse. [8]

Treatment

Effects of weight loss on lipids and lipoproteins

The NCEP-ATPIII recommends weight reduction as part of LDL-C–lowering therapy for overweight/obese persons. The NCEP notes that losing ~4.5 kg of body weight is projected to reduce LDL-C by 5 to 8%. In a meta-analysis of 70 weight loss studies that evaluated the effects of weight loss on lipids and lipoproteins, for every 1-kg decrease in body weight, there was a 1.93 mg/dL decrease in total cholesterol; a 0.77 mg/dL decrease in LDL-C; a 0.27 mg/dL increase in HDL-C during active weight loss; a 0.35 mg/dL increase in HDL-C with stabilized weight; and a 1.33 mg/dL decrease in TGs.[9]

Perhaps no lipid parameter responds better to nutritional intervention (and increased physical activity) than TG levels. The amount of weight loss affects the TG-lowering response, with greater weight loss resulting in a greater reduction. The type of nutritional intervention also is of significance, in that weight loss achieved in overweight patients by lower carbohydrate diets would be expected to lower TG more than weight loss achieved by higher carbohydrate diets. [10]

It is important to appreciate that during weight loss HDL-C may decrease below baseline, whereas after weight loss is maintained, HDL-C may increase above baseline. [9]

Exercise, lipids, and lipoproteins

There is a wide variation in the lipid response to exercise training; however, some studies have shown exercise-generated reductions in LDL-C of 4–7% as well as increases in HDL-C of 4% to 25% depending on baseline lipid values at training volumes of 1200-2200kcal/week. [11]

This volume of exercise (150 min or more per week, optimally 250–300 min per week or ≥2000 kcal per week) is similar to that recommended for long-term weight control. (12)

Any effect on lipids and lipoproteins of the intensity of exercise is small as compared with that of the volume of exercise, ie, kcal expended per week.This may be one reason

why many of the resistance training studies have shown little if any reduction in LDL-C and or TGs, as such training may induce inadequate energy expenditure. Some resistance training studies have reported slight-to-moderate reductions in total and LDL-C and others reporting no change. [13]

It is likely that the blood lipid response to strength training is related to total net energy expenditure of the session, as it is with aerobic endurance exercise. [14]

Exercise programs have also been shown to decrease fasting TGs by 4% to 37%.[15]

Medical Therapy

The choice of statin should depend principally on the LDL reduction and on the judgement of the treating physician. It should also be noted that the higher doses of statins may be moderately effective at reducing triglyceride levels (though not necessarily at raising HDL levels) and thus may reduce the need for combination therapy. With the use of statins, LDL levels may be reduced to 50 mg/dl. There is no safety data at such low LDL levels. The use of high-dose statin therapy (e.g., simvastatin 40 mg or atorvastatin 40 or 80 mg) to treat hypertriglyceridemia should be restricted to patients with both high LDL cholesterol levels and high triglyceride levels. Changes in therapy should be based on laboratory follow-up between 4 and 12 weeks after initiating therapy. Once goals have been achieved, laboratory follow-up every 6–12 months is suggested. [16]

Table (3): Lipid-Lowering agents [17]

Bile acidbinding resins	
Cholestyramine	4 g, 8 g , 12 g or 16 g twice daily
Colestipol (Colestid)	5 g twice daily or 30 g per day, in divided doses
HMG-CoA reductase	
inhibitors (statins)	
Atorvastatin	10 to 80 mg per day anytime
Rosuvastatin	5-40 mg per day
Fluvastatin (Lescol)	20 mg or 40 mg at bedtime, or 20 mgv
Lovastatin (Mevacor)	20 mg, 40 mg or 80 mg with evening meal
Pravastatin (Pravachol)	10 mg, 20 mg or 40 mg at bedtime
Simvastatin (Zocor)	5 mg, 10 mg, 20 mg or 40 mg at bedtime
Fibric acid analogs	
Clofibrate (Atromid-S)	500 mg four times daily
Gemfibrozil (Lopid)	600 mg twice daily
Fenofibrate	
Ezetimibe	10 mg twice daily

Multiple Drug Therapy:

An LDL level greater than 130 mg per dL (3.35 mmol per L) requires further reduction , and combination drug regimens are sometimes required .An additional cholesterol-lowering drug is probably required if the LDL cholesterol level remains above

the target level after three months of single-drug therapy. In patients with coronary heart disease , there is a great need to initiate cholesterol-lowering medication. Although drug therapy is not usually started until patients have undergone a three- to six-month trial of dietary therapy, in some patients with marked hypercholesterolemia or coronary heart disease, it is reasonable to initiate drug therapy earlier. (18)

Follow Up Of Drug Therapy:

Because of biologic and analytic variability of lipoprotein levels, it is advisable to obtain at least two lipoprotein levels during one to two months of maximum dietary therapy before beginning drug therapy. If it seems likely that pharmacotherapy will be needed, baseline liver function tests should also be performed. (18)

After starting the LDL cholesterol level should be measured in about six weeks and again in 12 weeks. Liver function and other tests for drug toxicity can be done at these times. If the LDL goal is reached, lipid levels should be checked every six to 12 months. Followup analysis should occur six to eight weeks after a change in drug therapy. (19)

Other Therapeutic Modalities

- Lifibrol

Lifibrol is a lipid-lowering agent presently under investigation. Clinical trials have shown that lifibrol lowers total cholesterol and LDL cholesterol levels with a potency similar to that of high-dose statins. Lifibrol has also been shown to reduce Lp**{*a*}**, fibrinogen and uric acid levels. Its effects on HDL cholesterol and triglyceride levels are less consistent. The mechanism of action of this agent is complex and probably multimodal. It appears to act at an earlier level of the cholesterol synthesis pathway than do the statins. Side effects are primarily gastrointestinal. (20)

- Gene Therapy:

Gene therapy is several years from clinical use. It may prove ideal for use in patients with genetic disorders such as familial hypercholesterolemia. Gene therapy will probably not be appropriate in dyslipidemic patients whose predominant risks for coronary heart disease is exogenous. (21)

- Plasmapheresis:

Plasmapheresis has become the most common nonpharmacologic, nondietary treatment of severe hypercholesterolemia. In nonselective plasmapheresis, the patient's plasma is replaced with salt-free human albumin. This action reduces triglyceride levels dramatically and decreases the risk of pancreatitis. (22)

- Surgical Modalities:

Partial ileal bypass that eliminates the reabsorption of bile acids at the distal portion of the ileum has been shown to be a viable treatment in some cases of severe dyslipidemia. Portacaval shunt and liver transplantation have been shown to be effective in treating severe hypercholesterolemia. These procedures, of course, are not first-line treatments. (23)

Thyroid gland

The thyroid dysfunction may be in the form of hyperthyroidism or hypothyroidism.

Hypothyroidism

Definition:

It is a clinical syndrome that results from reduced free T_3 and Free T_4 irrespective to the cause. [24]

Causes of hypothyroidism: [25]

Primary causes:

1. Iodine deficiency
2. Autoimmune diseases: (Hashimoto thyroiditis,Atrophic thyroiditis)
3. Iatrogenic causes:
   - Surgical removal.
   - External radiation.
4. Infiltrative diseases:
   - Lymphoma.
   - Amyloidosis.

Secondary causes:

1. Panhypopituitarism: Pituitary tumour, necrosis as in sheehan's syndrome.
2. Hypothalamic causes: Congenital, infections.

Table (4): Clinical manifistations of hypothyroidism [24]

1. Face:	• Puffy face. • Eye lid edema. • Pallor • Hair is dry, brittle. • Thining of the outer third of eye brows.
2. Skin:	• Dry, thin, nail growth is retarded.
3. Nervous system:	• Depression. • Parathesia. • Reduced memory. • Tendon jerks show slowed relaxation.
4. Cardiovascular system:	• Bradycardia. • Flat T wave. • Pericardial effusion.
5. Gastrointestinal tract:	• Constipation. • Achlorhydria.
6. Respiratory system:	• Pleural effusion. • Dyspnea. • Ventilatory response to hypoxia and hypercapnea are reduced.
7. Musculoskeletal system:	• Arthralyia • Joint effusions. • Muscle cramps. • Stiff muscles.
8. Hematological:	• Megaloblastic anemia.
9. Reproductive system:	• Decreased libido • Oligomenorrhea or amenorrhea. • Menorrhagia. • Galactorrhea.
10. Metabolic system:	• Hypothermia. • Hyperlipidemia (Increased serum cholesterol and triglycerides). • Weight gain despite decreased appetite.

Subclinical hypothyroidism

It is characterized by increased thyrotropin-stimulating hormone (TSH) levels in patients whose free thyroxine (T4) levels are not below normal.[26]

Although the condition may resolve or remain unchanged, within a few years in some patients, overt hypothyroidism develops. [25]

What happens to patients who are found to have an elevated TSH level without other findings? In some cases, the TSH level will be normal if measured again several months later; we would then attribute the initial elevation to laboratory error or, perhaps, to an episode of silent thyroiditis with a transient hypothyroid phase. In other cases, the subclinical hypothyroidism remains unchanged. The third possibility, progression to overt hypothyroidism, occurs at a rate of about 5 percent per year in patients with raised TSH levels and detectable antithyroid antibodies. In selected cases (e.g., elderly patients with high titers of antithyroid antibodies), the risk of progression to overt disease may be closer to 20 percent per year. Consideration of these possible outcomes affects the decision about whether to treat or to observe without treatment.[26]

Indications for treatment in subclinical hypothyroidism are not established, but general guidelines can be offered. Greater magnitude and duration of TSH elevation and higher titers of antithyroid antibodies increase the probability that the condition will progress to overt hypothyroidism and, therefore, increase the potential benefit of treatment with levothyroxine. The presence of symptoms that might be related to mild hypothyroidism also increases the potential benefit of treatment. Risk of harm to the patient, against which this potential benefit must be balanced, is quite small, since the use of the sensitive TSH assay provides assurance that we are not raising the blood thyroid hormone levels too much as long as TSH levels do not fall below the normal range. In patients with coronary artery disease and minimal elevations of TSH, however, it may be advisable to follow the TSH level rather than subject the patient to the small risk of levothyroxine therapy.[26, 27]

In short, it seems reasonable to treat patients who have a TSH level that is consistently elevated above 10 mU/L, especially if titers of antithyroid antibodies are increased. Also, patients who complain of fatigue, dry skin, constipation, muscle cramps or other common symptoms of hypothyroidism may possibly benefit from treatment even if their TSH level is elevated only into the 5 to 10 mU/L range. An algorithm summarizing this approach is presented in the following figure.[26, 27]

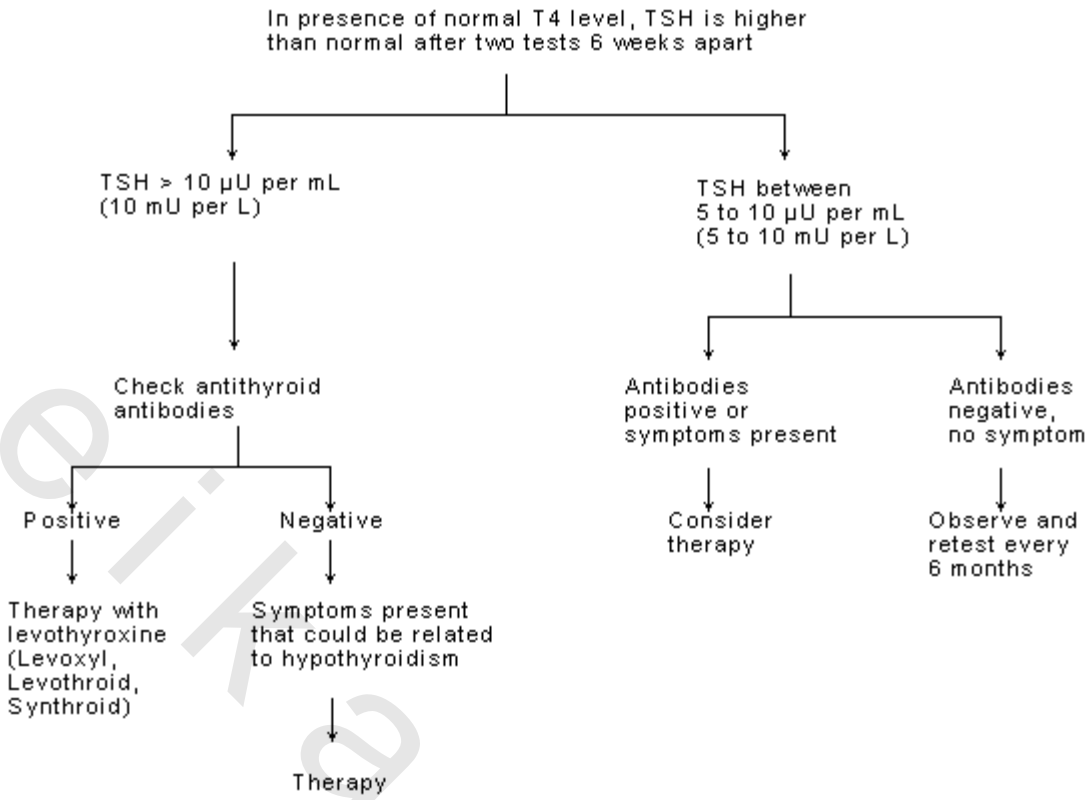

Figure (1): Algorithm for treatment of SHO

Treatment is similar to that recommended in patients with overt hypothyroidism. Levothyroxine is the agent of choice.[27]

The average daily replacement dosage of levothyroxine is 75 to 125 µg, or about 1.6 µg per kg per day. Treatment is commonly initiated with 25 to 50 µg daily and raised by increments of 25 to 50 µg.[27]

Laboratory evaluation of hypothyroidism:

A normal TSH level excludes primary (not secondary) hypothyroidism. If TSH is elevated, a free T_4 level is needed to confirm the presence of clinical hypothyroidism, but free T_4 is inferior to TSH when used as a screening test, as it will not detect subclinical or mild hypothyroidism. [25]

Hyperthyroidism

Definition:

Hyperthyroidism is the condition resulting from the effect of excessive amount of thyroid hormone on the body tissues. [24]

Causes: [28]

I. Primary hyperthyroidism:

1- Grave's disease:
Caused by the production of auto antibodies that stimulate the thyroid stimulating hormone (TSH) receptors leading to excessive production of thyroid hormones.
2- Toxic multinodular goiter:
3- Toxic adenoma.
4- Sub acute thyroiditis (De Quervain"s):
Caused by virus infection (e.g: enteroviruses)
5- Iatrogenic: Thyroid hormone intake.

II. Secondry hyperthyroidism:

1- Pituitary adenoma secreting TSH hormones.
2- Drugs: amiodarone, interferone.

Subclinical Hyperthyroidism

It is characterized by a low or undetectable concentration of serum thyrotropin (TsH) with free triiodothyronine (FT_3) and free thyoxine (FT_4) levels within laboratory reference ranges. [29]

Patients with mild hyperthyroidism suffer from palpitations, tremors, heat intolerance, sweating, nervousness, anxiety, inability to concentrate. [30]

Subclinical hyperthyroidism may be caused by exogenous or endogenous factors , and may be transient or persistent. . The exogenous form of subclinical hyperthyroidism is usually related to TSH-suppressive therapy with l-thyroxine (l-T4) for a single thyroid nodule, multinodular goiter, or differentiated thyroid carcinoma. In addition, TSH may be unintentionally suppressed during hormone replacement therapy in about 20% of hypothyroid patients . The endogenous form is usually related to the same causes as overt thyrotoxicosis, namely Graves' disease, autonomously functioning thyroid adenoma, and multinodular goiter.[31]

Administration of the cardioselective β-blocker bisoprolol for 6 months significantly improves the mean symptom rating scale score in patients with exogenous subclinical hyperthyroidism, mostly because this treatment attenuates many signs and symptoms mimicking adrenergic overactivity. Moreover, treatment for 6 months with methimazole significantly improved symptoms evaluated with the Wayne index in endogenous subclinical hyperthyroid patients, paralleling the normalization of the thyroid status.[32, 33]

Clinical manifestations of hyperthyroidism [25]

1. Eye: Lid retraction causing staring appearance.
2. Skin: Warm, moist, orange-peel thickening of peritibial area.
3. Nervous system: insomnia, impaired concentration, fine tremors, hyperreflexia, muscle wasting and proximal myopathy.
4. Cardio vascular system: Angina, heart failure, sinus tachycardia and atrial fibrillation.
5. Reproductive system: Oligominorrhea, gynaecomastia.
6. Haemopoiesis: Pernicious anemia.
7. Musculoskeletal system: Atrophic weak muscles, myasthenia graves.
8. Gastrointestinal tract: Increase appetite and hyper defecation.
9. Body weight: Weight loss despite good appetite.

Insulin sensitivity

Definition:

It is the ability of insulin to lower blood glucose concentration by stimulating glucose uptake and suppressing its production. (34)

Insulin insensitive persons therefore,have high plasma insulin level,and this compensatory state of hyperinsulinemia is a marker of insulin resistance syndrome. (35)

This syndrome can be defined as a cluster of abnormalities including obesity,hypertension,dyslipidemia and type 2 diabeties. (36)

Insulin resistance syndrome is a multisystem disorder that is associated with multiple metabolic and cellular alterations.

Metabolic disturbances that commonly occur in patients with insulin resistance syndrome is atherogenic dyslipidemia, hypertension, glucose intolerance and prothrombotic state. (37)

Atherogenic dyslipidemia is characterized by three lipoprotein abnormalities: elevated VLDL, small LDL particles and decreased HDL cholesterol levels (the lipid triad). (37)

The prothrombotic state is characterized by increased fibrinogen level, increased plasminogen activator inhibitor (PAI)-1,and different abnormalities in platelet function. (38)

Pathophysiology:

The mechanisms that are responsible for the insulin resistance syndrome (IRS) include genetic or primary target cell defects, autoantibodies to insulin and accelerated insulin degradation. Not all tissues require insulin action to transport glucose into the cells. However, some tissues, particularly skeletal muscles and adipocytes, are extremely dependent on insulin for glucose transport. For insulin to act, it must first bind to a specific receptor on the cell surface of all insulin target tissues. (39)

Once insulin is bound to its receptor, it triggers a cascade of intracellular events, culminating in the movement of a protein called glucose transporter (GLUT4) from its intracellular location to the cell surface where it binds and transport glucose into the cells**.** Glucose transporter (GLUT4) is the main insulin responsive transporter, cellular action of insulin involves a wide variety of effects on postreceptor signaling pathways within target cells. The beta subunit of insulin receptor is a tyrosine kinase, which is activated when insulin binds to the alpha subunits, the kinase activity autophosphorylates and mediates multiple action of insulin. (40)

Decreased activity of any of these steps could be responsible for insulin resistance. Multiple sites of defects in the action of insulin have been identified, each resulting in the failure of the glucose transport mechanism, which leads to mild hyperglycemia. The latter stimulates the islet cells, leading to compensatory hyperinsulinaemia. (41)

Two major variants of insulin receptor abnormalities that are associated with acanthosis nigricans have been described; the classic type A insulin resistance syndrome due to absence or dysfunctional receptor and type B resulting from auto-antibodies to insulin receptor. Both are associated with hyper insulinaemia. [42]

Etiology of insulin resistance: [43]

(1) Abnormal B-cell secretory product:

* Abnormal insulin molecule.
* Incomplete coversion of proinsulin to insulin.

(2) Circulating insulin antagonists:

* Hormonal antagonist.
* Non hormonal antagonist as:
  - Cytokines.
  - Metabolites (free fatty acid and glucose).
  - Anti-insulin antibodies.
  - Anti-insulin receptor antibodies.
  - Insulin degrading enzymes (insulinases).

(3) Target tissue defects:

* Insulin receptor defects.
* Post-receptor defects.

Insulin resistance can be linked to obesity especially central abdominal obesity, hypertension, type 2 diabetes mellitus, dyslipidemia and coronary atherosclerotic heart disease, and other abnormalities as hyperuricaemia, dysfibrinogenemia and microalbuminuria. [44,45]

Measurement of insulin sensitivity:

It is calculated as a product of fasting insulin (uIU/ml) multiplied by fasting plasma glucose level (mmol/L) over constant value equal to 25. [46]

The lack of practical, inexpensive, reliable serum tests means that the diagnosis of insulin resistance can, at best, be made on the basis of strong clinical suspicion, factors that are associated with increased likelihood of insulin resistance:

- Strong family history.
- History of gestational diabetes.
- Polycystic ovary syndrome.
- Impaired glucose metabolism.
- Obesity: body mass index of 30kg/m² or more.
- Increased W/H ratio: 1.0 in men and 0.8 in women. [37]

Thyroid disease is associated with various metabolic abnormalities, due to the effects of thyroid hormones on nearly all major metabolic pathways. Thyroid hormones regulate the basal energy expenditure through their effect on protein, carbohydrate, and lipid

metabolism. This might be a direct effect or an indirect effect by modification of other regulatory hormones such as insulin or catecholamines. [47] Dyslipidemia is a common metabolic abnormality in patients with thyroid disease, either in the overt or subclinical forms of the disease, and constitutes the end result of the effect of thyroid hormones in all aspects of lipid metabolism leading to various quantitative and/or qualitative changes of triglycerides, phospholipids, cholesterol, and other lipoproteins. [48]

Hypothyroidism and dyslipidemia:

In hypothyroidism, although decreased thyroid function is accompanied by reduced activity of HMG-CoA reductase, TC and LDL-C levels are increased in patients with overt hypothyroidism. [49-53] This is due to the decreased LDL-receptors' activity, resulting in decreased catabolism of LDL and IDL. [54]

Moreover, a decrease in LPL activity is found in overt hypothyroidism, decreasing the clearance of TG-rich lipoproteins. [55] Therefore, overt hypothyroid patients may also present with elevated TG levels associated with increased levels of VLDL and occasionally fasting chylomicronemia. [51-54]

Hypothyroid patients may also exhibit elevated levels of HDL-C [49] mainly due to increased concentration of HDL_2 particles. Indeed, due to a reduction of hepatic lipase activity a decrease in HDL_2 catabolism is observed. [56] Moreover, decreased activity of the cholesterylester transfer protein (CETP) results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL-C levels. [57]

Subclinical hypothyroidism (SHO), is a far more common disorder than overt hypothyroidism. [31,58]

SHO is associated with increased levels of TC and LDL-C. [59] In addition, some studies have shown that SHO dyslipidemia may also be accompanied by increased TGs [60, 61] and decreased HDL-C levels. [62] Moreover, subjects with high normal TSH levels , but with positive antithyroid antibodies may also exhibit elevated cholesterol levels. [63]

Thyrotoxicosis and dyslipidemia:

The incidence of hyperthyroidism is lower (2.2%) compared with hypothyroidism in the general population. Similarly, a decreased prevalence of hyperthyroidism is evident in hyperlipidemic patients. [64]

Despite the increased activity of the HMG-CoA reductase, levels of TC, LDL-C, ApoB and Lp(a) tend to decrease in patients with clinical or subclinical hyperthyroidism. This is due to increased LDL receptor gene expression resulting in enhanced LDL receptor-mediated catabolism of LDL particles. [65,66]

A decrease in HDL-C levels is also observed in hyperthyroidism, due to increased CETP-mediated transfer of cholesteryl esters from HDL to VLDL and increased HL-mediated catabolism of HDL_2. Triglyceride levels remain unchanged. [65,66]

Thyroid hormones and insulin sensitivity (resistance):

Thyroid hormones exert both insulin agonistic and antagonistic actions in different organs. However, this occurs in a fine balance necessary for normal glucose metabolism. Decreased or excess of thyroid hormones can break this equilibrium leading to alterations of carbohydrate metabolism. [67]

Thyrotoxic subjects frequently show impaired glucose tolerance. This is a result of increased glucose turnover with increased glucose absorption through the gastrointestinal tract, postabsorptive hyperglycemia, elevated hepatic glucose output, with elevated fasting and/or postprandial insulin and proinsulin levels, elevated free fatty acid concentrations and elevated peripheral glucose transport and utilization. [68]

Subclinical hypothyroidism (SHO) and overt hypothyroidism (OH) are established risk factors for insulin resistance, hyperlipidemia, hypercoagulability and low grade inflammation. [69,70] Several studies have proved the association between insulin resistance and overt hypothyroidism, but there is controversy as to whether this association is also present in subclinical hypothyroidism. The prevalence of thyroid disease in patients with diabetes is significantly higher than that in the general population. [71] This indicates a possible interplay between thyroid status and insulin sensitivity.

Insulin resistance leads to an increased production of hepatic cholesterol and very low density lipoproteins (VLDL) [72] and an increased HDL cholesterol (HDL-C) clearance. [73] Insulin resistance augments the deleterious effect of hypothyroidism on the lipid profile. [74]

Clinical hyperthyroidism is often accompanied by abnormal glucose tolerance and insulin resistance. [68,75-77] In approximately 50% of patients with hyperthyroidism, glucose tolerance disorders were observed, and 2–3% of patients had diabetes. In non-diabetic subjects, normal or increased fasting insulin, peptide C and proinsulin concentrations are observed, which is indicative of moderate peripheral insulin resistance. [78] This is associated with an increased insulin resistance in the liver, aggravation of general peripheral insulin resistance, and increased glucose uptake in muscles.

Overt hyperthyroidism increases the demand for insulin. It is associated with accelerated metabolism, tissue resistance to insulin and increased insulin degradation. In thyrotoxicosis, increased glucose absorption occurs in the digestive tract which is attributed to a higher rate of stomach emptying and increased blood flow in the portal vein, which leads to postprandial hyperglycaemia, characteristic of hyperthyroidism. [79]

The effect of thyroid hormones on hepatocytes is antagonistic to insulin and stimulates glucose production in the liver.

Clinical hypothyroidism is considered to be an insulin resistance risk factor. [75, 80–84] In hypothyroidism, a decrease in the intestinal glucose absorption rate occurs, along with a decrease in the adrenergic activity leading to a reduction in liver and muscle glycogenolysis, as well as a decrease in gluconeogenesis and baseline insulin secretion. [75, 78] However, a postprandial increase in insulin secretion against the background of generalized peripheral insulin resistance has been observed, associated with a higher concentration of free fatty acids, reduced glucose uptake and increased glucose oxidation.[78]