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An Overview on Drug Induced Metabolic Syndrome: A Review

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ABSTRACT

Metabolic syndrome is now a day more common and serious disease that has been recognized relatively recently. Metabolic syndrome was originally described by Reaven as "syndrome X" or "insulin resistance syndrome in 1988. Metabolic syndrome represents a cluster of related metabolic abnormalities, including central obesity, hypertension, dyslipidemia, hyperglycemia, and insulin resistance, with central obesity and insulin resistance in particular recognized as causative factors. Metabolic syndrome as a manifold risk factor for developing cardiovascular diseases and nowadays publics and health providers are more aware of such a health risk. The use of medication for various clinical conditions and its association of developing metabolic syndrome have been identified.

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BACKGROUND

Metabolic syndrome is now a day more common and serious disease that has been recognized relatively recently. Metabolic syndrome was originally described by Reaven as "syndrome X" or "insulin resistance syndrome in 1988.A global transition in the disease pattern has been observed where the related impact of infectious diseases decreasing while lifestyle disorders like CVD and Diabetes are increasing dominating the disease pattern. Epidemiologist in India and international agencies like WHO, IDF and NCEP-ATPIII have been recognised as an alarming burden of CVD for the past 15 years. It is estimated that by 2020, CVD will be the largest cause of disability and death in India.[1]

Metabolic syndrome represents a cluster of related metabolic abnormalities, including central obesity, hypertension, dyslipidemia, hyperglycemia, and insulin resistance, with central obesity and insulin resistance in particular recognized as causative factors.[3] Widely accepted definitions for the diagnosis of MS (Table 1) include criteria developed by the National Cholesterol Education Program's Adult Treatment Panel III (ATP III), the International Diabetes Federation (IDF), and the American Heart Association/National Heart Lung and Blood Institute (Harmonization) .[2]In addition to serving as a predictive tool for the development of cardiovascular disease and type 2 diabetes, MS identification allows for the development and evaluation of targeted lifestyle interventions to combat the rising burden of non-communicable diseases.[3]

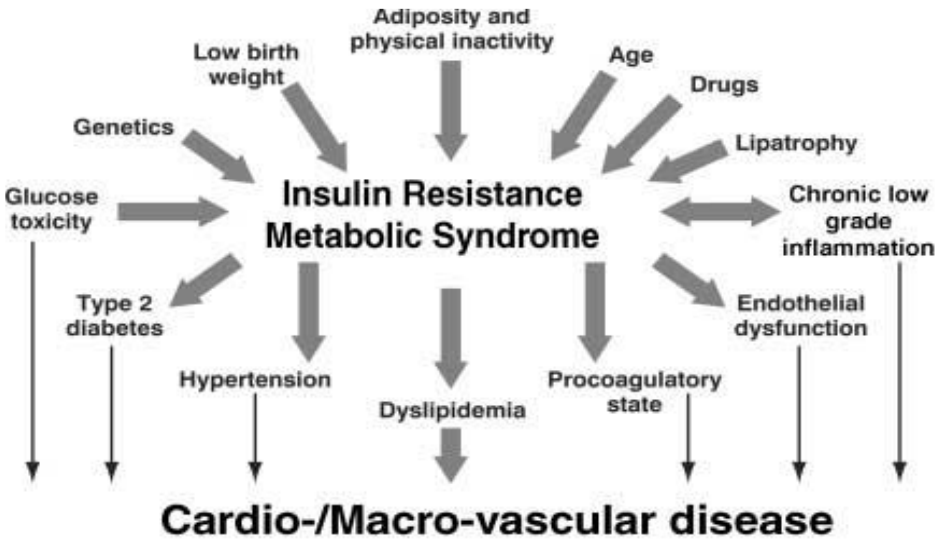
Table 1. Definitions of metabolic syndrome

	NCEP ATP III (2005 revision)	WHO (1998)	EGIR (1999)	IDF (2005)
Absolutely required	None	Insulin resistance* (IGT, IFG, T2D or other evidence of IR)	Hyperinsulinemia† (plasma insulin >75th percentile)	Central obesity (waist circumference‡): ≥94 cm (M), ≥80 cm (F)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes, plus two of the five criteria below	Hyperinsulinemia, plus two of the four criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m²	Waist circumference: ≥94 cm (M), ≥80cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl or HDL-C: <35 mg/dl (M), <39 mg/dl (F)	TG ≥177 mg/dl or HDL-C <39 mg/dl	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx			HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or Rx	≥140/90 mmHg	≥140/90 mmHg or Rx	>130 mmHg systolic or >85 mmHg diastolic or Rx
Other criteria		Microalbuminuria†		

*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.
†Urinary albumin excretion of ≥20 μg/min or albumin-to-creatinine ratio of ≥30 mg/g.
‡Reliable only in patients without T2D.
§Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.
Rx, pharmacologic treatment.

A study done in urban part of eastern india , calculated prevalence rate as 43.2% (n=509) , out of which it is found that women have higher rate of 52.2% (n=307) and men 34.2% (n=202).[4]

The underlying etiology of metabolic syndrome is overweight, obesity, adiposity and physical inactivity, low birth weight, age, drugs, lipotrophy, low grade inflammation and genetic predisposition. Some medications are also identified that may increase the risk of developing metabolic syndrome by either promoting weight gain, altering lipid level or by glucose metabolism. Figure: 1 represents the various risk factors and consequences associated with Metabolic syndrome.[5]



The metabolic syndrome is associated with increased risk of variety of disease outcomes, including diabetes, peripheral arterial disease, fatty liver and non alcoholic steatohepatitis, polycystic ovarian syndrome, gallstones, asthma, sleep apnoea, malignant disease.[4]

Some medications are also identified that may increase the risk of developing metabolic syndrome by either promoting weight gain, altering lipid level or by glucose metabolism.Table.2. represents some medications that may increase the risk of the Metabolic Syndrome.[1]

Table.2: List of some medication which may increase the risk of Metabolic Syndrome

Antihypertensive agents
β Blockers
Diuretics
Endocrinologic agents
Corticosteroids
Danazol
Growth hormone
Oral contraceptives
Thiazolidinediones
Neurologic/psychiatric agents
Antipsychotics
Antiepileptics

ANTIHYPERTENSIVE AGENTS:

Hypertension is a strong contributor to cardiovascular disease in patients with the cardiometabolic syndrome. Over the last few decades, a number of classes of anti-hypertensive drugs have been used to treat hypertension, with the ultimate goal of reducing the incidence of endpoints such as heart attacks and stroke.[6] The association between obesity and hypertension may be related to greater insulin resistance, leptin-mediated enhancement of sympathetic activity, sodium and fluid retention, adipocyte-mediated effects on angiotensin II, and atrial natriuretic peptide levels.[7]Patients with hypertension have an increased prevalence of type 2 diabetes mellitus and impaired glucose tolerance.[8,9]Hypertension, obesity, and diabetes or prediabetes cluster together in the metabolic syndrome.[10,11]

Some of the broad categories of antihypertensives include thiazide diuretics, ARBs, ACEIs, CCBs and β-blockers.Numerous reports have associated adverse metabolic effects such as glucose intolerance and lipid abnormalities with the use of diuretics and β blockers.[12] These agents are among the most prescribed agents used for the treatment of hypertension and CV disease, and thus it is important to consider their potential effects on the metabolic syndrome and to weigh the potential risk against the benefits shown in long-term clinical trials. [13]It has been hypothesized that some of the medications used to treat hypertension might have

metabolic effects that negate some of the benefits that would be expected from decreases in blood pressure. Increases in blood glucose during antihypertensive treatment have been found to be a predictor of myocardial infarction.[14] Insulin resistance is also associated with endothelial dysfunction, which is predictive of future cardiovascular events. [15]

THIAZIDE DIURETICS

Thiazide diuretics are recommended for consideration as initial therapy in the treatment of primary hypertension, as multiple clinical trials have proven benefit in the reduction of morbidity and mortality.[13] In the Systolic Hypertension in the Elderly Program (SHEP),16 participants on the thiazide-based regimen had an increase in the risk of new-onset diabetes compared with placebo, but noted a decrease in CV events.[16]

Several studies reported that the use of thiazide diuretics has contributed to insulin resistance and worsening glycemic control in diabetes. Earlier studies reported that there is an association of potassium with blood glucose level both in glycemic as well as nonglycemic subjects.[13] Most of the Studies state that lower potassium predicted the magnitude of FBG change in patients initiated on thiazide treatment.[17].Proposed mechanism of developing metabolic syndrome was an increasing change from baseline serum insulin levels as a consequence of increasing body mass index.[18]

The factors responsible for the production of mineralocorticoids are several pro and anti-inflammatory cytokines present in adipose tissue. The use of diuretics will augment the release of aldosterone which causes insulin resistance along with the release of inflammatory cytokines. Thiazides along with its action on inducing mineralocorticoids, also has an property of increasing locally active and circulating cortisol. Thus the mixed action of inducing both mineralocorticoids and glucocorticoids by thiazides enhances the adipocyte's inflammatory signals, leading to obesity, insulin resistance and glucose intolerance.[13]

β-BLOCKERS:

The other group of drug which is most commonly used for the management of hypertension as initial therapy is the beta blockers. In several studies of nonselective [19] or β 1 selective [20,21,22] -blockers, there was significantly decreased insulin sensitivity in hypertensive patient. The Atherosclerosis Risk in Communities Study (ARIC)[23]demonstrated that among hypertensive

patients, β-blocker therapy was associated with a 28% increased risk of developing type 2 diabetes compared with no antihypertensive therapy.[1]

Several mechanisms are involved in the development of insulin resistance by the use of β-blockers. In metabolic syndrome states such as Type2 diabetes and obesity, endothelium dependent insulin mediated vasodilatation is impaired leading to insulin resistance.[13]

Normally, insulin promotes vasodilatation which results in increased blood flow thereby increases the glucose uptake by the skeletal muscles. But during the treatment of non-selective β-blockers, the unopposed α_1 activity causes vasoconstriction leading to decreased blood flow to muscles. This might result in decreased insulin stimulated glucose uptake and insulin resistance.

Pancreatic β_2 receptors are responsible for insulin secretion and by the use of β-blockers these receptors are blocked resulting in impairment of insulin secretion thereby impairing glucose metabolism leading to hyperglycemia.[13]

Weight gain is the other factor which further impairs insulin sensitivity by the use of β-blockers. It has been reported in certain studies that the use of non-selective and β1-selective β blockers have little effect on total cholesterol and LDL-C levels but lead to a reduction in HDL-C and increased triglycerides. Studies suggest that there will be decreased enzyme activities related to lipid metabolism which will alter the insulin secretion and removal that may reduce peripheral blood flow.[24]

Therefore, in metabolic syndrome weight gain – insulin resistance interaction are found to be the leading cause tor developing severe vasoconstriction that further worsen the glucose levels due to the use of β-blockers.[25]

ENDOCRINOLOGIC AGENTS:

Commonly used endocrinological agents in daily practice are corticosteroids, mineralocorticoids and oral contraceptives. Corticosteroids and their biologically active synthetic derivatives have different actions in carbohydrate, protein and lipid metabolism. [26]Electrolyte regulating activities of mineralocorticoids maintains fluid and electrolyte balance; and preservation of normal function of the cardiovascular system, the immune system, the kidney, skeletal muscle, the endocrine system, and the nervous system.[27]

Corticosteroids and their biologically active synthetic derivatives differ in their metabolic (glucocorticoid/stress hormone) and electrolyte-regulating (mineralocorticoid) activities. [28]These agents are employed at physiological doses for replacement therapy when endogenous production is impaired.[30] In addition, glucocorticoids potently suppress inflammation, and their use in a variety of inflammatory and autoimmune diseases makes them among the most frequently prescribed classes of drugs.[31,32]

Generally, the physiologically relevant mechanisms such as hepatic and peripheral insulin resistance, dyslipidemia, obesity and hyperglycemia occur across the tissues which contribute to the metabolic abnormalities which are represented in Fig.1.[29]

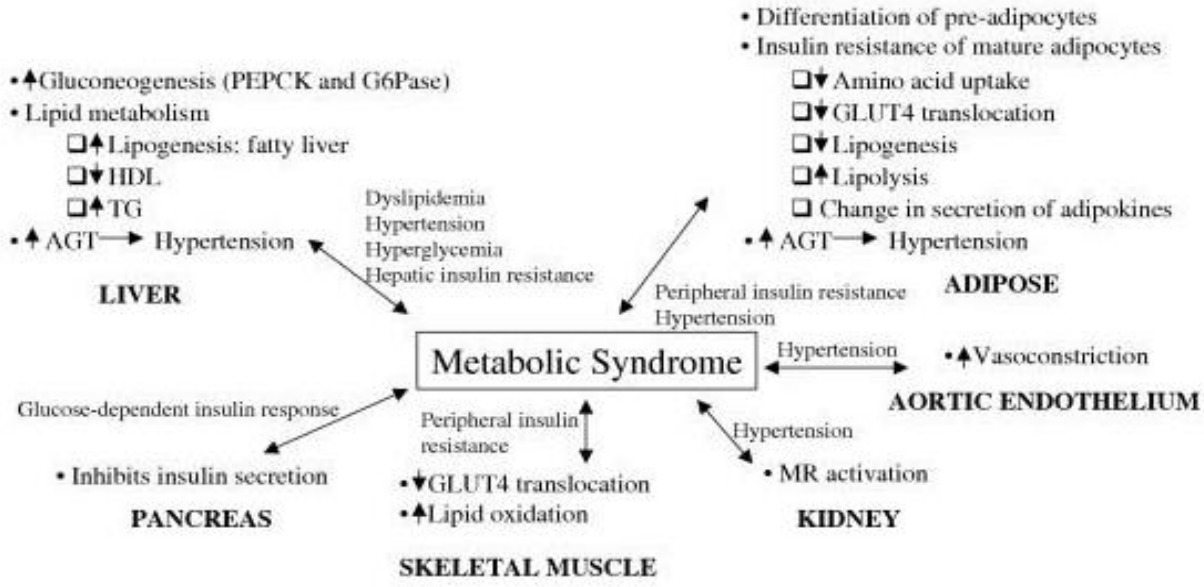


Fig:2 The link between the metabolic effects of glucocorticoids and the features of the Metabolic Syndrome. The major effects in different tissues are summarized and the potential physiological links to the Metabolic Syndrome are shown

Clinical finding supports that glucocorticoids therapy causes triglyceride accumulation in the liver as they have a role in activating the enzymes that is responsible for fatty acid synthesis and lipoprotein secretion.[29] These hepatic fats will contribute the further pathophysiological process of metabolic syndrome. They promote a negative regulation of hepatic insulin sensitivity and produce certain features of the metabolic syndrome which is independent of visceral fat mass.

Other mechanism for developing metabolic syndrome features is by activation of Glucose Receptor (GR) by glucocorticoids.[29] The glucose receptors are responsible for the activation of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), the rate-limiting enzymes in gluconeogenesis [34,35] and thus induce the hepatic gluconeogenic pathway, thus causes excessive glucose production and hyperglycemia.

A homogenous mechanism can be seen in adipocytes and skeletal muscles inducing insulin resistance by glucocorticoids.[29]

In adipose tissue, a differentiation of pre-adipocyte to adipocyte occurs which is initiated by glucocorticoids, resulting in increased body fat mass. The adipocytes, thus differentiated will also produce insulin resistance by decreasing the uptake of insulin-stimulated glucose without causing any change in the insulin binding capacity in the presence of glucocorticoids. [34]Glucocorticoid also antagonises the insulin –mediated translocation of glucose transporters from intracellular compartments to the plasma membrane which will produce decreased insulin sensitivity. The insulin-stimulated amino acid uptake by adipocytes is also inhibited in the presence of glucocorticoids. [35]

In skeletal muscle, there will be an increased lipolysis and lipid oxidation which could result in peripheral insulin resistance induced by glucocorticoids.In pancreas, glucocorticoids will inhibit the insulin secretion from B-cells resulting in hyperglycemia. [34]

Glucocortioids are also involved in developing hypertension which is one among the metabolic syndrome criteria. GC has a mineralocorticoid receptor (MR) mimetic action. In kidney, both 11β-HSD1 and 11β-HSD2 expression are balanced and thereby the interconversion of inert and active GCs are maintained. Thus the MR activation is maintained tissue-specifically. Under excessive GC there will be increased 11β-HSD1 or decreased 11β-HSD2 activity that will result in MR activation leading to sodium-water retention and thus hypertension. The 11β-HSD1 expression is also consistent in aortic endothelial cells which are also a pathogenesis for GC induced hypertension.[29]

The possible mechanism of the effect on the lipid profile is complex. One theory suggest an increase in TG due to the redistribution of body fat by corticosteroid treatment to the upper trunk and face with a loss of fat in the extremities, giving a “buffalo like” torso [36,37]This will result in with fewer glucocorticoid receptors in cells which will stimulate both lipolysis and lipogenesis.[38]This causes an accumulation of glucose as a result of few receptors. This will

also cause an increase in TG as a result of increased insulin level.[39]GC causes increase in VLDL level, lipogenesis, synthesis and secretion of apolipoprotein in liver. GC also inhibits fatty acid β-oxidation. [40]

Some former studies reports the central role of GCs through Hypothalamus-Pitutory-Adrenal axis involvement in developing obesity and other features of the Metabolic Syndrome.[41] The exaggerated effects of glucocorticoid induced metabolic disturbances can be analysed by measuring the glucose homeostasis and hepatic lipid markers.[42]

ORAL CONTRACEPTIVES

One of the widely applied method for contraception as well as for management of certain diseases in post menopausal women.[43]They have been shown to alter lipid levels among different population groups with various dyslipidemia patterns.[44]Progestogens and combined oral contraceptives containing 'second generation' progestogens are some drugs that adversely affect the lipid profile pattern. They increase total cholesterol, low density lipoprotein cholesterol and triglycerides by up to 40, 50 and 300%, respectively, and decrease high density lipoprotein cholesterol by a maximum of 50%.[45] On the other hand, estrogens, hormone replacement therapy, combined oral contraceptives containing 'third generation' progestogens, selective estrogen receptor modulators shows mostly beneficial effects on the lipd profile. [46]

Oral contraceptives cause insulin resistance by increasing plasma insulin level and produces glucose intolerance. This effect is primarily due to progestin activity affecting carbohydrate metabolism.[47,48]

Estrogen shows a protective effect, and has a positive effect on lipid profile. They lower TC (2-10%) and LDL-C levels (7-20%) and increase HDL-C levels (5-20%) in a dose-related manner.[49,50] Progestins opposes estrogen induced lipid changes and shows an opposite effect on TC and HDL-C.[51,52,53,54]The androgenic effects of progestin are responsible for the varying serum lipid level. The serum lipid level depends more specifically on the potency of estrogen and the androgenicity of the progestin of the oral contraceptives used.

Women on OCs should be advised to check lipid profiles regularly.[55]This is of prime significance for women who are at more risk for the development of the metabolic syndrome.

ANABOLIC STEROIDS

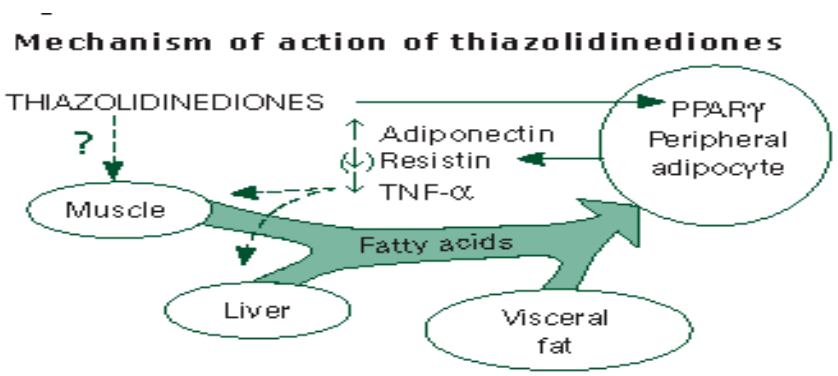
For the management of endometriosis and fibrocystic breast disease and for hereditary angioedema prophylaxis, a synthetic steroid Danazol is used.[56] Certain review datas showed that during danazol treatment there is a rapid reduction in HDL-c by upto 50% and increase in LDL-C by 10-40%.[57-61] The possible mechanism behind this was its effects on hepatic lipase, LDL receptor, and lecithin cholesterol acyl transferase activity. Some datas also reported an alteration in lipoprotein level who were under danazol treatment. [62] The reports were also consistent that upon stopping treatment the lipid levels will become normal. However the people on prolonged therapy for 12 months or above were at a high risk for developing CV disease.[63]

THIAZOLIDINEDIONES

Thiazolidinediones/Gliptans are intended to reduce insulin resistance by increasing peripheral glucose disposal and decreasing glucose production. Commonly used thiazolidinediones are pioglitazone and rosiglitazone and both of them have variable effects on lipids with type2 DM. Reports of earlier studies shows that pioglitazone was having greater effect on triglycerides, HDL-C, Non –HDL-C and LDL particle size when compared to rosiglitazone regardless of their common mechanism in glycemic control.[62]

Thiazolidinediones binds eagerly to peroxisome proliferator-activated receptor gamma in adipocytes particularly adionectin to promote adipogenesis and fatty acid uptake peripherally and not in visceral fat. Thus the drug will improve the patient's insulin sensitivity by reducing the circulating fatty acid concentrations and lipid availability in liver and muscle.

The effect of the thiazolidinediones on lipid concentrations is complex.The mechanism of action of thiazolidinediones is given below on Fig 3:



Thiazolidinediones bind to the gamma form of the peroxisome proliferator-activated receptor (PPARγ). This stimulates peripheral adipocytes to increase their uptake of free fatty acids, which leads to reductions in the fat stored in muscle, liver and visceral fat deposits. The thiazolidinediones also lead to an increase in the secretion of adiponectin and a decrease in the production of resistin and tumour necrosis factor α (TNF-α). It is unknown if thiazolidinediones have direct effects on muscle or liver.[63]

Most of the other biological effects of the thiazolidinediones are potentially beneficial and related to improvements in parameters of the insulin resistance syndrome (Table 3).

Table 3: Additional biological effects of the thiazolidinediones 7

Increased HDL cholesterol concentrations
Increased LDL cholesterol concentrations
Increased LDL cholesterol particle size
Reduced triglyceride concentrations (particularly pioglitazone)
Small reduction in blood pressure
Reduced incidence of microalbuminuria
Decrease in plasminogen activator inhibitor-1 and fibrinogen
Vasorelaxation
Increase in vascular reactivity
Anti-inflammatory effects
All of these effects, except for increased LDL cholesterol concentrations, would be regarded as potentially beneficial in regard to the metabolic syndrome and cardiovascular disease.

Besides the beneficial effects of thiazolidinediones, it produces weight gain and increased peripheral fat mass due to adipocyte differentiation and proliferation, particularly in peripheral adipocytes. Fluid retention is the other moderate to severe adverse effect which results by the use of thiazolidinedione therapy. This may result in peripheral oedema especially in those patients who are under concomitant insulin therapy. [62]

ANTIEPILEPTICS

Antiepileptic medications are used in several treatment areas like seizure disorders, different psychiatry disorders, severe headaches, migraine and diabetic neuropathy etc. Antiepileptic

medications along with sedentary lifestyle are more prone to develop obesity and metabolic syndrome.Several studies had reported the effects of antiepileptic drugs on metabolic and lipid profiles along with the incidence of obesity.[65]

Among the different antiepileptic medication, previous studies explored that valproic acid have more tendency to develop metabolic syndrome and weight gain. [1]Several mechanisms are involved for weight gain, which include certain genetic factors, increased insulin and proinsulin levels, increased appetite by their hypothalamic involvement, sedentary lifestyle with less energy expenditure, hyperleptinemia and leptin resistance. But some other studies reported that valproic acid decreases leptin levels in a dose dependent manner by reducing the leptin mRNA levels in adipocytes without affecting mRNA degradation. Therefore valproic acid was found to have fluctuating leptin levels.[66]Valproic acid also has an interaction with adinopectin which has a major role in maintaining insulin sensitivity and glucose homeostasis.[67]

Studies reported that valproic acid when compared to other antiepileptics, shows an increase in fasting blood sugar level. [65]They suggested that valproic acid have a property of interfering with insulin metabolism in liver but will not induce or promote insulin secretion. Other mechanism of VPA for hyperinsulinemia and insulin resistance is by the action of increased free fatty acid levels. Increased FFA levels leads to impairment in insulin synthesis and elevates the proinsulin-insulin secretion ratio, thus develops insulin resistance.[67]

ANTIPSYCHOTICS

Antipsychotic medications now become the widely used treatment options for various psychotic conditions like schizophrenia, depression, bipolar disorders and developmental disorders. [1,71]

Typical or first generation antipsychotics were used previously but presently its use is restricted due to its extrapyramidal side effect. Atypical or second generation antipsychotics are now a dayused widely for treating psychotic disorders. But atypical antipsychotics are associated with weight gain, dyslipidemia and insulin resistance. Most common prevalence among these conditions is the weight gain.[68]

The various atypical antipsychotics used now a day are clozapine, olanzepine, resperidone, qietiapine, aripiprazole and ziprasidone. Among these dysregulation of glucose homeostasis

[hyperglycemia and insulin resistance] independent of weight gain and adiposity has been defined in conjunction with clozapine and olanzapine.[69]

The real mechanism of antipsychotics inducing weight gain and metabolic alterations are unknown.[70] Studies revealed the involvement of dopaminergic, serotonergic and histaminergic neurotransmission along with changes in neuro-endocrine systems and neuopeptides which cause weight gain.[72]

Leptin, an obese gene is responsible for regulating appetite and energy expenditure and its increased levels results in obesity.[1,71]Among the atypical antipsychotics, clozapine and olanzapine shows an increased affinity to H1 action that results in over eating than other drugs such as aripiprazole and risperidone.

The mechanism of antipsychotic inducing hyperglycemia and hyperlipidemia were found to be the antagonistic action on 5HT2C receptor on pancreatic cell resulting in insulin resistance and increased TG level. These effects are more commonly shown by olanzapine and clozapine.[73]

IMMUNOSUPPRESSANTS

Most commonly used immunosuppressant for post transplant treatment are calcineurin inhibitors, (cyclosporine and tacrolimus), sirolimus and mycophenolate mofetil (MMF) and less commonly azathioprine. Usually long term immunosuppression with one or more of the above drugs are given as post transplant drugs and each drug has its own metabolic side effects or complication but is dose dependent.[74]

According to a Cochrane review tacrolimus shows an increased risk of producing post transplant diabetes when compared to cyclosporine.[75,76,77,78]It was reported that calcineurin inhibitors produces their diabetogenic effects by inhibiting pancreatic β –cell function and decreasing insulin production.It also decreases peripheral glucose uptake thus causing peripheral insulin resistance.[80]

Both tacrolimus and cyclosporine produces dyslipidemia but it was studied and reported that cyclosporine causes more short-term weight gain, than the other one. The mechanism involved in producing Hyperlipidemia is by decreasing bile acid synthesis thereby reducing cholesterol transport to bile. Cyclosporine also produces effect in regulating the circulating levels of LDL cholesterol by binding to LDL cholesterol receptors.[1]

Another category of immunosuppressant producing metabolic consequences are m-TOR inhibitors (sirolimus, everolimus) which produce complex interaction in lipid and glucose metabolism. They interfere in triglyceride synthesis which has been thought to be associated with decreased adipocyte cell proliferation. They also decrease the uptake of lipids and fatty acid uptake thus producing reduced weight gain. Long term therapy with sirolimus promotes gluconeogenesis and decreased insulin clearance in liver. It also reduces lipoprotein lipase activity and also interferes with insulin dependent adipocyte triglyceride storage.[74]

CONCLUSION

Metabolic syndrome as a manifold risk factor for developing cardiovascular diseases and nowadays publics and health providers are more aware of such a health risk. The use of medication for various clinical conditions and its association of developing metabolic syndrome have been identified. Therefore care should be taken during the selection of drugs in every patients especially those who are obese or at risk for developing diabetes or cardiovascular disease.

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