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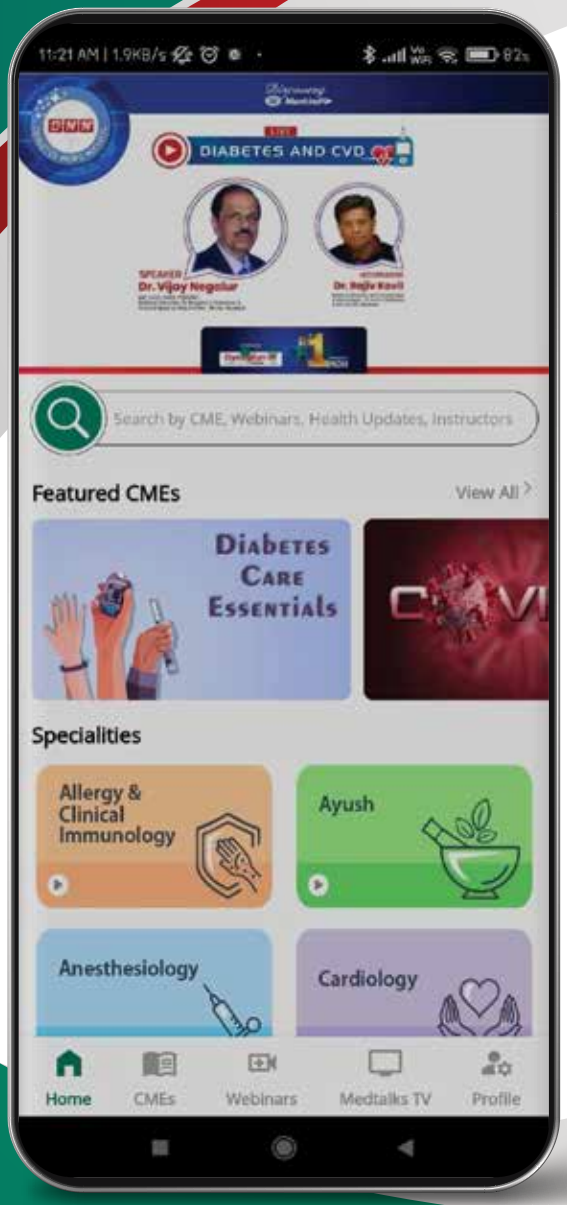

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CLINICAL STUDY

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ORIGINAL STUDY

CASE REPORT

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Serum Uric Acid Levels and Risk of Gestational Diabetes

Increase in serum uric acid levels prior to 24 weeks of gestation has been linked to risk of gestational diabetes mellitus (GDM) in an observational study recently published in the *Journal of Clinical Endocrinology and Metabolism*.[1]

Researchers retrospectively analyzed data of pregnant women with singleton pregnancies from February 2018 to June 2022 to investigate the association between serum uric acid levels before 24 weeks of gestation and subsequent odds of GDM and other adverse pregnancy outcomes.

Out of the 24,023 women included in the study, 3,204 (13.34%) developed GDM between 24 and 28 weeks of gestation. A strong association was observed between uric acid levels and risk of GDM, the primary outcome of the study. The relative risk for GDM was 1.43 among women with uric acid levels ranging from 240-300 μmol/L. The relative risk increased to 1.82 with rise in serum uric acid levels more than 300 μmol/L. A similar association was observed between serum uric levels and the secondary outcomes of the study, which were GDM type A2 requiring medication for optimal glycemic control, preterm birth and GDM combined with preeclampsia.

These findings show that detection of elevated uric acid levels before 24 weeks of gestation is associated with risk of gestational diabetes. The study further suggests that "the best time to test for uric acid is before 18 weeks of gestation". Hence, monitoring of uric acid levels in early pregnancy may identify women at risk of GDM allowing early intervention.

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Risk Factors for "At-Risk Foot" in Diabetes

Diabetic foot is an ominous complication of diabetes. Diabetic neuropathy and peripheral arterial disease predispose to diabetic foot disease leading to amputation of the foot in due course of time, a process, which may be hastened by infection. Early identification of the "at-risk foot" in these patients may prevent development of a diabetic foot ulcer.

A study involving 3030 Chinese adults with type 2 diabetes attempted to examine the prevalence and factors affecting the at-risk foot in patients with diabetes.

These patients had been a part of an at-risk foot screening program in Shanghai from March 2021 through to April 2021. Data for the study was collected via questionnaires, physical examination and laboratory investigations.

Analysis of data revealed the presence of at-risk foot in almost 28% of the patients with diabetes included in the study. The chances of having at-risk foot increased with advancing age, higher urine albumin creatinine ratio (UACR) and reduced eGFR with odds ratios of 1.04, 1.00 and 0.99 respectively.

Eleven percent of patients with diabetes had peripheral artery disease. While age, pulse rate and low-density lipoprotein cholesterol (LDL-C) were independently associated with elevated risk for peripheral artery disease, factors such as eGFR, lymphocyte-to-monocyte ratio and high-density lipoprotein cholesterol (HDL-C) were found to be protective. There was no association between levels of glycosylated hemoglobin (HbA1c) and the risk of severe peripheral artery disease.

This study highlights the high prevalence of at-risk foot in diabetes patients. It has also delineated risk factors that are associated with increased risk of having at-risk foot, of which, the most significant risk factors were older age and renal impairment. Presence of these risk factors should alert the clinician about an impending diabetic foot and take proactive measures to prevent its occurrence.

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REVIEW ARTICLE

Hydroxychloroquine - An Antimalarial and Anti-inflammatory Drug

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A B S T R A C T

Hydroxychloroquine – a quinoline antimalarial, has hypoglycemic effects that manifest due to its action on the intracellular insulin metabolism in peripheral tissues. Recent studies confirm that the use of Hydroxychloroquine can aid in preventing new onset diabetes and complications of diabetes, systemic lupus erythematosus and rheumatoid arthritis, as well as in improving the mortality rate of these patients.

Keywords: Hydroxychloroquine, T2DM, DMARD, antimalarial, diabetes

Introduction

Hydroxychloroquine has been widely used as a first-line drug for treating malaria and inflammatory disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Interestingly, recent evidence suggests that this agent can improve glycemic control in patients with diabetes via inhibition of insulin degradation and its protective action against insulin resistance. Furthermore, it has been documented that hydroxychloroquine use can aid in lowering the risk of diabetes, improving the serum lipid profile of type-2 diabetes mellitus (T2DM) patients and reducing their predilection to developing cardiovascular complications.

Hydroxychloroquine is a derivative of chloroquine and belongs to the drug class 4-aminoquinoline that has immunosuppressive, antimalarial, anti-inflammatory and anti-rheumatologic actions. It is a disease-modifying anti-rheumatic drug (DMARD) and is often used in the treatment of malaria, SLE and RA. This agent is highly active against the erythrocytic forms of *Plasmodium vivax, P. ovale, P. malariae* and susceptible strains of *P. falciparum*.

Hydroxychloroquine was approved by the DCGI in the year 2014, as an adjunctive treatment of T2DM as a third-line therapy, along with lifestyle and nutritional modifications, for patients with inadequate glycemic control despite sulfonylurea and metformin combination treatment. This drug is also found to be preventive against the development of type-2 diabetes (T2D) in patients with RA and SLE and can be used as a preventive measure for T2DM.[1] Recent studies confirm that the use of hydroxychloroquine can aid in preventing new-onset diabetes and complications of diabetes, SLE and RA, as well as in improving the mortality rate of these patients.

Effect of Hydroxychloroquine on Glucose Metabolism

Hydroxychloroquine – a quinoline antimalarial, has hypoglycemic effects that manifest due to its action on the intracellular insulin metabolism in peripheral

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tissues. The hypoglycemic effect of hydroxychloroquine has been recorded in T2DM patients as well as in those without a history of diabetes. Researchers have demonstrated that hydroxychloroquine can be used as an adjunctive drug with sulfonylurea and with insulin, for lowering the glycosylated hemoglobin (HbA1c) in T2D patients. In fact, the antihyperglycemic potential of this drug has been compared to pioglitazone. When compared to other immune suppressants like methotrexate, hydroxychloroquine has shown to render a greater reduction in HbA1c within 12 months of initiating treatment. Furthermore, this agent can lower fasting glucose and prevent incident diabetes even in non-diabetic individuals.[2]

Researchers speculate that hydroxychloroquine causes alterations in insulin metabolism and signaling through cellular receptors, and thus, renders favorable metabolic effects on glucose control and lipid profiles.[3,4]

Hydroxychloroquine is categorized as a conventional or non-biological DMARD. A new multicenter cohort study published in *PLoS One* assessed the factors associated with incident diabetes in patients with RA who received glucocorticoids.

The findings revealed that the incidence rate of diabetes was lowest for patients using hydroxychloroquine and TNF inhibitors. Moreover, the glucocorticoid treatment and obesity elevated the risk of incident diabetes, which could be prevented with the use of DMARDs.[5]

Comparative Benefits of Hydroxychloroquine

RA and psoriasis predispose to insulin resistance and diabetes mellitus. Hydroxychloroquine therapy has shown to prevent the occurrence of diabetes in this patient population.

A retrospective cohort study that included 13,905 patients observed that when compared to other conventional DMARDs, the adjusted risk of newly recorded diabetes was lower among patients of RA or psoriasis who were started on hydroxychloroquine therapy.[6]

A 2014 double-blinded, randomized study published in *Current Medical Research and Opinion* compared efficacy and safety of hydroxychloroquine with pioglitazone in T2D patients. Here, 267 patients with uncontrolled T2DM on 3 months' treatment with of glimepiride/gliclazide and metformin were either given hydroxychloroquine 400 mg/day or pioglitazone 15 mg/day in conjunction, for 24 weeks.

It was found that the mean reductions in HbA1c levels at week-12 and -24 were comparable between patients receiving hydroxychloroquine and pioglitazone. Additionally, lower levels of triglycerides were recorded in both the intervention groups at week-24. Moreover, hydroxychloroquine therapy was well-tolerated; it was stated that hydroxychloroquine could be used as an adjunctive treatment in the management of uncontrolled T2D.[7]

When compared to dyslipidemia monotherapy with atorvastatin, combination treatment with atorvastatin and hydroxychloroquine has shown to confer lower incidence of diabetes cases in prediabetic individuals.

In addition, percentage reductions in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and non-high-density lipoprotein cholesterol (HDL-C) were significantly greater in the combination treated group after 24 weeks. Hence, hydroxychloroquine has also been found to be efficacious when used along with other antihyperglycemic drugs and statins.[8]

Efficacy When Used Alone or as Concurrent Medication

Sufficient evidence confirms the efficacy of hydroxychloroquine in the prevention of incident diabetes, as well as atherosclerosis and cardiovascular disease in patients with inflammatory disorders. In severe RA cases, hydroxychloroquine is preferred as part of combination therapy.[9]

A 2013, systematic review that aimed to characterize conditions which responded to treatment with hydroxychloroquine reported on its therapeutic effects in a wide range of disorders – diabetes mellitus, dyslipidemias, coagulopathies, infectious diseases and malignancies.

It was stated that actions of this drug may also be beneficial in patients without rheumatic conditions, such as in diabetes mellitus and viral infections.[10]

Prior evidence suggests that hydroxychloroquine lowers HbA1c in diabetes patients with and without rheumatic disease.[11] Additionally, researchers have found that hydroxychloroquine use can provide better glycemic control in sulfonylurea refractory patients with poorly controlled T2D.[12]

In the year 2015, the results of a double-blinded, randomized trial suggested that hydroxychloroquine could emerge as a potential drug for combination with statins in the treatment of dyslipidemia. It has also shown to prevent incident diabetes in prediabetic and healthy individuals with inflammatory disorders.[8]

Furthermore, this agent can be used as an adjunctive therapeutic option in patients with T2D that is uncontrolled despite the use of two-drug oral hypoglycemic agent (OHA) regimens.

Hydroxychloroquine benefits in reducing the HbA1c and the dose of insulin in patients with T2D. This drug is found to be safe and efficacious in patients with and without inflammatory disorders and its effects are comparable to other OHAs like pioglitazone.[7]

Mechanism of Action and Pharmacology

Mechanisms of action responsible for the efficacy of hydroxychloroquine in ameliorating diabetes and other related disorders, such as dyslipidemias, coagulopathies and infectious diseases include:

- Altered signaling through cellular receptors
- Changes in levels of inflammatory mediators
- Inhibition of autophagy
- Antibody production
- Selective presentation of self-antigens
- Post-glycosylation modifications of infectious agents.[10,13]

Hydroxychloroquine accumulates in lysosomes and autophagosomes of phagocytic cells and causes changes in the intra-endosomal acidity; impacts the production of proinflammatory cytokines; modulates antioxidant activity; and protects against cytokine-mediated cartilage resorption. Hence, this drug is effective in treating SLE, RA and osteoarthritis.[14]

Hydroxychloroquine is an immunosuppressant that inhibits the production of rheumatoid factor and acute phase reactants of RA. It also inhibits collagenase and proteases—enzymes directly responsible for cartilage breakdown.[15]

Hydroxychloroquine can improve glycemic control in patients with diabetes via inhibition of insulin degradation and its protective action against insulin resistance.[16] Scientists also speculate possible favorable effects of hydroxychloroquine on the histological structure of the pancreas, as well as the metabolic profiles of individuals with diabetes mellitus that could be expressed due to its anti-inflammatory action.[17]

Additionally, hydroxychloroquine has an antithrombosis effect, owing to the reduced platelet aggregation by this drug and its protection of the annexin A5 anticoagulant shield from disruption by aPL antibodies.[13]

Hydroxychloroquine is rapidly absorbed in the upper gastrointestinal tract following oral administration. It is partially metabolized by the liver. The drug is dealkylated by cytochrome P450 enzymes into its active metabolite; it is excreted by the kidneys and takes up to 3-6 months to reach its maximal therapeutic efficacy.[15]

Prevention of Complications by Hydroxychloroquine

Cardiovascular disease is associated with substantial mortality among patients with RA, dyslipidemia, and diabetes mellitus. The results of a 2016 retrospective study showed that among 547 RA patients who were given hydroxychloroquine, only three suffered a cardiovascular event, compared to 99 events in 719 non-users of hydroxychloroquine. Overall, a 72% decrease in the risk of incident cardiovascular disease (CVD) was recorded in RA patients with the use of hydroxychloroquine, likely due to its antiplatelet action.[18]

Hydroxychloroquine alleviates risk factors of CVD, such as dyslipidemia and diabetes. In addition, it is said to have a protective effect against endothelial dysfunction and accelerated atherosclerosis.[13] Hydroxychloroquine exhibits the potential to render beneficial changes in lipid profiles – LDL-C and TC.

The use of this drug can also reduce the risk of thrombotic events in patients with lupus and antiphospholipid syndrome.[18] The anti-thrombosis effect of this drug has been observed in SLE patients with and without antiphospholipid antibodies. In premenopausal SLE women, hydroxychloroquine use has been associated with significantly lower aortic stiffness.[13]

Its antihyperglycemic effect is dose-dependent. In patients with SLE, beneficial effects of hydroxychloroquine have been documented on target organ damage and survival. In addition, its use has shown to confer lesser cerebrovascular damage on brain MRIs of this patient population.[13,19]

Newer findings

In patients with inflammatory disorders, for instance RA or SLE, the use of hydroxychloroquine antagonizes the hyperglycemic effect of glucocorticoids.[19,20,21] A recent study published in the *QJM* found that patients with Sjogren's syndrome who were treated

with hydroxychloroquine had a significantly lower cumulative incidence of new-onset diabetes mellitus compared those who did not receive this drug. This effect was found to be dose-dependent and on long-term (3 years) use, this agent exhibited significant protective effects.[22]

Conclusion

Hydroxychloroquine has been found to be effective in a wide spectrum of disorders that includes metabolic diseases, for example, diabetes and dyslipidemia; inflammatory conditions like SLE, RA and Sjogren's syndrome; and infections, such as malaria. Hydroxychloroquine has shown added benefits in patients who are at a high risk for developing CVD, such as those with SLE, RA and diabetes. Hydroxychloroquine prevents the occurrence of cardiovascular events through its reduced platelet aggregation, control of TC and LDL-C, and antithrombotic and preventive effects on atherosclerosis. Large number of recent studies confirm the preventive role of hydroxychloroquine in new-onset diabetes mellitus among individuals with RA, SLE, obesity or prediabetic status, as well as in healthy individuals. This drug can be safely used in gestating mothers as it does not impose any harm to the fetus and improves pregnancy outcome in those with inflammatory disorders.

Meanwhile, hydroxychloroquine can be used along with other DMARDs, statins, OHAs and insulin. Results from clinical trials indicate a comparable efficacy of hydroxychloroquine and other OHAs like pioglitazone. In fact, researchers approve of its adjunctive use in patients with T2D who exhibit refractory hyperglycemia despite being on a two-drug OHA regime.

The use of OHA also aids in reducing the dose of insulin in patients with T2D. Furthermore, it prevents complications like dyslipidemia, CVD and cerebrovascular damage in those who are at high risk, for instance, patients with diabetes, SLE or RA, and therefore, reduces target organ damage and improves the survival rate of these patients.

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■■■■

REVIEW ARTICLE

Medication Reconciliation

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A B S T R A C T

The Institute of Medicine (IOM) stated that preventable medication errors are the most common type of errors in healthcare. It is of fundamental significance when building a safer care continuum, as it highlights the reason for continuous and more vigilant medication reconciliation and required effort at all interfaces of care, including community. Without a robust medication reconciliation process, the potential for catastrophic outcomes remains a constant concern. Prevention of medication errors is essential through strategies that are based in evidence of medication reconciliation strategies on medication errors in community.

Keywords: Medication errors, healthcare delivery system, medication reconciliation, adverse drug reaction, quality improvement

Introduction

Medication safety is a significant issue in hospitals and throughout healthcare. Great improvements are needed, and hospitals are engaged in many efforts to reduce errors and increase this aspect of patient safety. Nurses are the most involved at the medication administration phase, although they provide a vital function in detecting and preventing errors in the prescribing, transcribing and dispensing stages too. Administration errors constitute a significant proportion of all errors, yet, there isn't much known about the causes or about the effectiveness of proposed solutions.

Research addressing the complex process of medication use in hospitals is the need of the hour and requires a new approach to produce valid knowledge from studies done in the field with few controls of confounding factors. There is a large and growing body of research addressing medication safety in healthcare.

Medication Errors

Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patient or consumer is termed a medication error. These events may be associated with professional practice, healthcare products, procedures and systems, including prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring and use.

Some of the factors associated with medication errors include the following:

- Medications with similar names or similar packaging
- Medications that are not commonly used or prescribed
- Commonly used medications to which many patients are allergic (e.g., antibiotics, opiates and nonsteroidal anti-inflammatory drugs).

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Error-Prone Processes

There are five stages of the medication process: (a) ordering/prescribing, (b) transcribing and verifying, (c) dispensing and delivering, (d) administering and (e) monitoring and reporting. Monitoring and reporting is a newly identified stage about which there is little research. Some of the most noted hospitalized patients suffer preventable injury or even death as a result of adverse drug events (ADEs) associated with errors made during the prescribing, dispensing and administering of medications to patients.

Nurses are primarily involved in the administration of medications across settings. Nurses can also be involved in both the dispensing and preparation of medications (similar to pharmacists), such as crushing pills and drawing up a measured amount for injections. Preliminary research on medication administration errors (MAEs) reported an error rate of 60%. Medication errors have been reported mainly in the form of wrong time, wrong rate or wrong dose. In other studies, approximately one out of every three ADEs were attributable to nurses administering medications to patients.

Medication Error-Prevention Strategies

Medication errors are common in hospital settings. To limit and mitigate these errors, it is necessary to have a thorough knowledge of the medication-use process in the emergency department and develop strategies targeted at each individual step. Some of these strategies include medication-error analysis, computerized provider-order entry systems, automated dispensing cabinets, barcoding systems, medication reconciliation, standardizing medication-use processes, education and emergency-medicine clinical pharmacists.

Nurses' Education and Training

Lack of medication knowledge is a constant problem, and there is a need to continually gain more knowledge about current and new medications. Nurses with more education and experience may have greater knowledge of medications.

Educational Strategies Aimed to Improve Medication Safety and Avert Unnecessary Medication Errors

Educational and training programs on drug therapy are required for medical/paramedical students, drug prescribers (doctors) and nurses (administering drugs) to reduce drug errors and to improve patient safety. A systematic approach is urgently needed to decrease organizational susceptibility to error, through providing required resources to monitor, analyze cause of errors and implement preventive strategies to reduce them.

A proper functioning national standardized system for medication errors detection and reporting using a unified terminology all over the country is necessary to allow for better knowledge sharing and practice change.

Medication Reconciliation

Medication reconciliation is a process that matches a patient's current hospital medication regimen against a patient's long-term medication regimen.

Or

Medication reconciliation is the process of comparing an individual's medication orders to all of the medications that the individual has been taking. It is a process that is an integral part of safety for older adults living in their homes in community settings.

Medication reconciliation is flexible enough to enhance hospital specific workflows and keep current on new information (Medication Reconciliation) relating to prescription medications and their reactions while supporting and exceeding the Patient Safety Goals, i.e.,From admission, transfer and discharge to post visit patient care, including community.

Medication reconciliation simplifies the process of reconciling a patient's medication therapy across the continuum of care. Healthcare system (HCS) works with hundreds of hospitals across the nation to simplify and streamline medication reconciliation. While every hospital has a goal of improving patient safety and saving time, every hospital is unique with its policies, protocols and guidelines.

Solutions of Medication Reconciliation

- Obtain a patient's prior medication history including medication fill and refill information and previous visit information.
- Analyze prior medication history.
- Provide medication transfer and discharge reports electronically or through printed media.
- Provide discharge prescriptions including patient medication education.
- Communicate and link directly to existing hospital clinical information systems.
- Identify high risk patients for medication nonadherence and obtain fill/refill information for clinicians use in follow-up visit.

HCS medication reconciliation has been proven to save time and increase accuracy during medication reconciliation:

- 2.4 more critical medications identified during admission
- 50% increase in computerized physician order entry
- 51-minute reduction in time to reconcile
- 23% increase in ordered critical medications.

Components of medication reconciliation include:

- Medication procurement
- Medication knowledge.

Medication procurement

- How and where the patient obtains and refills prescriptions?
- How the patient pays for the medications?
- Whether or not medication doses are ever missed due to lack of funds?

Steps for self-medication management

- Assessing the patient's knowledge of dose and frequency of medications
- Special instructions related to medications
- Medication mode of action
- Side effects to monitor and report
- Monitoring with each change in medication regimen.

Medication Knowledge

- Provide educational materials including medication instructions written in large letters and in bullet or list format, use of medication schedules and tailored instructions on how medications should be taken.
- Patients also need to understand the importance of communicating any changes in their medications to their healthcare providers.
- Patients should be encouraged to bring the medication list with them to physician visits to encourage medication reconciliation, and the list should be updated when medications are added or discontinued.
- Pharmacists can help empower patients by teaching them what it means to be an alert consumer and involved in their healthcare.

Medication reconciliation is centred on the safety principle of independent redundancy. Independent redundancy is a process whereby more than one care provider checks to make sure procedural steps are completed correctly.

Current Medication Proforma (For Medication Reconciliation)

Current medications	Dose	Route	Frequency	To be continued during hospital stay	Patient/ Family teaching
				Yes/No	Yes/No
				Yes/No	Yes/No
				Yes/No	Yes/No
				Yes/No	Yes/No
				Yes/No	Yes/No

The specific issues most in need of research (QI-Quality Improvement activities) are as follows:

- Barcoding and other medication safety technology—widely recommended, but little or no valid research using before-and-after designs.
- Independent RN double-checks—logical and widely recommended, but no research has been done describing, let alone testing, the effects of this policy.
- Relationship between nurse staffing and medication errors—a few descriptive studies and studies asking RN perceptions of the problem suggest that staffing and workload are major factors, but there are no research studies using valid and reliable data.
- Techniques to reduce distractions, interruptions, other risk factors for medication error need to be tested.
- Methods of effective education in medication safety for nurses and all care providers.
- Effectiveness of implementing new checklists, policies and procedures.
- Understanding work-arounds.
- Methods and techniques for successful implementation of system and process change.

Conclusion

Medication safety for patients is dependent upon systems, process and human factors, which can vary significantly across healthcare settings. Hence, corrective actions should target priority areas and root causes to prevent recurrence. There is a need of quality-improvement programs that focus on educating the staff about medication errors and the importance of reporting.

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■■■■

CLINICAL STUDY

Study of Thyroid Function Tests in Patients with Metabolic Syndrome

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ABSTRACT

Background: The metabolic syndrome is a constellation of clinical and metabolic abnormalities including abdominal obesity, hypertension, dyslipidemia and impaired fasting glucose or impaired glucose tolerance. Metabolic syndrome and thyroid dysfunction are independent risk factors for cardiovascular disease. **Aims and objectives:** To study the prevalence, symptomatology of thyroid dysfunction and fine needle aspiration cytology (FNAC) findings of thyroid in the patients having metabolic syndrome. **Material and methods:** The study was carried out in 60 cases of metabolic syndrome (according to NCEP ATP III criteria) selected from the medicine outdoor clinic (including diabetic clinics, thyroid clinics) and medicine indoor wards in Post Graduate Department of Medicine, SN Medical College and Hospital, Agra. Diagnosis of thyroid dysfunction was made by history, examination and serum FT4 and TSH. **Result and observations:** Out of 60 patients of metabolic syndrome, 30 patients (50%) were euthyroid, 13 patients (21.66%) had subclinical hypothyroid and 12 patients (20%) had overt hypothyroid. Five patients (8.33%) of metabolic syndrome had hyperthyroidism. Truncal obesity was most prevalent (80.0%) component of metabolic syndrome, followed by hypertriglyceridemia (70%). Diabetes mellitus was equally prevalent in both males as well as females and was present in about 40.0% patients and 53% of patients with metabolic syndrome were hypertensive. **Conclusion:** This study shows that 50% metabolic syndrome patients had thyroid dysfunction. About 21.66% had subclinical hypothyroidism, 20% had overt hypothyroidism and 8.33% were having hyperthyroidism. The most common symptom in metabolic syndrome patients with hypothyroidism was lethargy/sleepiness followed by dry and coarse skin. The most common symptom in hyperthyroid patients was nervousness (100%) followed by sweating, heat intolerance and palpitation in 80% of the patients.

Keywords: Metabolic syndrome, subclinical hypothyroid, hypothyroid, hyperthyroid

Introduction

The metabolic syndrome is a constellation of clinical and metabolic abnormalities including abdominal obesity, hypertension, dyslipidemia and impaired fasting glucose or impaired glucose tolerance. All these manifestations are surrogate markers of insulin resistance which is the crux abnormality associated with metabolic syndrome. Thyroid hormones markedly stimulate the basic metabolic rate and the metabolism of carbohydrate, lipids and proteins. This hormone appears to serve as a general pacemaker accelerating metabolic process and may be associated with metabolic syndrome. It also plays an important role in the development of the reproductive system. As metabolic syndrome and thyroid dysfunction (subclinical or overt hypothyroidism and hyperthyroidism) are independent risk factors for cardiovascular disease, it is possible that patients suffering from both these disease entities may have a compounded risk.

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Aims and Objectives

The aim of this study was to determine the prevalence, symptomatology of thyroid dysfunction and fine needle aspiration cytology (FNAC) findings of thyroid in the patients having metabolic syndrome.

Material and Methods

In our study, 60 patients of metabolic syndrome without liver disease (viral, alcoholic, drug, autoimmune, etc.), chronic renal disease, pancreatitis and pregnancy were studied. Their clinical (age, sex, family history and blood pressure), biochemical (thyroid-stimulating hormone [TSH], free thyroxine [FT4], lipid profile, blood sugar) and thyroid FNAC profiles were studied. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) at least three of the following criteria should be present to diagnose metabolic syndrome:

- Elevated waist circumference: Men - ≥90 cm for Indians, Women - ≥80 cm for Indians.
- Elevated triglycerides: ≥150 mg/dL.
- Reduced HDL ("good") cholesterol: Men - <40 mg/dL, Women - <50 mg/dL.
- Elevated blood pressure: ≥130/85 mmHg.
- Elevated fasting glucose: ≥110 mg/dL.

The thyroid hormone assays (FT4 and TSH) were done using enzyme-linked immunosorbent assay (ELISA), and fasting blood sugar, triglycerides and high-density lipoprotein cholesterol (HDL-C) were done enzymatically on Roche Automated Clinical Chemistry Analyzer.

Diagnosis of thyroid dysfunction was made by FT4 and TSH - *Euthyroid:* normal TSH and normal FT4; *Subclinical hypothyroidism:* high TSH and normal FT4; *Hypothyroidism:* high TSH and low FT4 and *Hyperthyroidism:* low TSH and high FT4.

Observations and results

Our study group consisted of 24 male (40%) and 36 (60%) female patients. Male-to-female ratio was 2:3. Majority of patients (40.0%) belonged to age group 40-49 years. Mean age of all the patients was 47.6 ± 7.5 years. The mean age of males and females was 49.6 ± 8.0 and 46.2 ± 7.1, respectively.

The prevalence of components of metabolic syndrome (Fig. 1) in men and women were, central obesity in 18 (75%) and 30 (83.3%) patients, respectively; low HDL-C in 12 (50%) and 28 (77.8%) patients, respectively; high triglycerides in 18 (75%) and 24 (66.7%), respectively; impaired fasting glucose (>100 mg/dL) or diabetes in 12 (50.0%) and 12 (33.3%), respectively and elevated blood pressure in 18 (75%) men and 32 (88.9%) women.

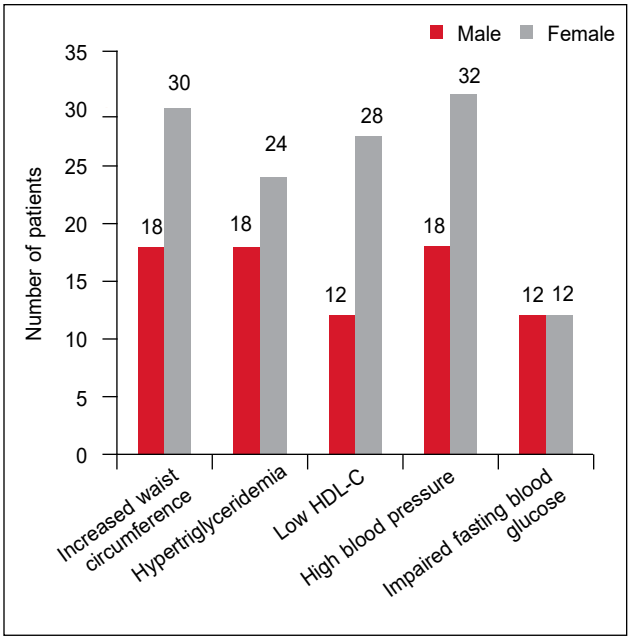

Figure 1. Different components of metabolic syndrome in the study group.

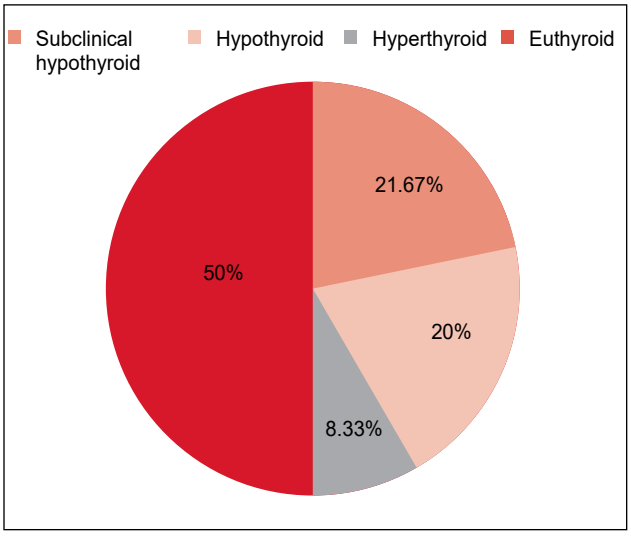

Figure 2. Thyroid dysfunction in study group.

Out of 60 patients of metabolic syndrome (Fig. 2), 30 patients (50%) were euthyroid, 13 patients (21.66%) had subclinical hypothyroid and 12 patients (20%) had overt hypothyroid while 5 patients (8.33%) had hyperthyroid.

The most common symptom (Table 1) in both subclinical and overt hypothyroid patients was (77.77%)

Table 1. Prevalence of Symptomatology of Hypothyroidism in the Study Group

Symptoms	Male (n = 4)		Female (n = 14)		Total (n = 18)	
	No.	%	No.	%	No.	%
Lethargy/ Sleepiness	3	75	11	78.57	14	77.77
Dry and coarse skin	3	75	10	71.42	13	72.22
Cold intolerance	2	50	10	71.42	12	66.66
Puffiness of face	2	50	10	71.42	12	66.66
Body aches	2	50	8	57.14	10	55.55
Weight gain	2	50	7	50	9	50
Constipation	2	50	9	64.28	11	61.11
Depression	2	50	8	57.14	10	55.55
Paresthesia	2	50	6	42.85	8	44.44
Menorrhagia	-	-	5	35.71	5	27.77
Thyroid gland size enlarged	1	25	5	35.71	6	33.33
Hair loss	1	25	4	28.57	5	27.77

Table 2. Prevalence of Symptomatology of Hyperthyroidism in the Study Group

Symptoms and signs	Male (n = 2)		Female (n = 3)		Total (n = 5)	
	No.	%	No.	%	No.	%
Nervousness	2	100	3	100	5	100
Sweating	2	100	2	66.66	4	80
Hypersensitivity to heat	1	50	3	100	4	80
Palpitation/ Increased heart rate	2	100	2	66.66	4	80
Fatigue	1	50	2	66.66	3	60
Goiter	1	50	2	66.66	3	60
Hyperdefecation	1	50	1	33.33	2	40
Weight loss	1	50	2	66.66	3	60

lethargy (sleepiness) followed by dry and coarse skin (72.22%), cold intolerance (66.66%), puffiness of face (66.66%), constipation (61.11%), depression (55.55%) and body aches (55.55%). Weight gain was seen in 50% and paresthesia in 44.44% hypothyroid patients. Thyroid gland size was enlarged in (33.33%) 6 patients. Five hypothyroid females (35.71%) had menorrhagia. Hair loss was present in 5 patients (27.77%).

The total number of hyperthyroid patients was 5 in the study. The commonest symptom (Table 2) was nervousness (100%) in our patients. Other symptoms like sweating (80%), hypersensitivity to heat (80%) and palpitation (80%) were also common in these patients. Fatigue, weight loss and enlarged thyroid (goiter) were present in 3 patients (60%). One male and 1 female hyperthyroid patient had hyperdefecation.

Twelve thyroid dysfunction patients with metabolic syndrome underwent FNAC of thyroid gland. Out of 12 patients, 8 patients (66.66%) had normal cytological findings. Two (1 subclinical hypothyroid and 1 overt hypothyroid) patients had simple colloid goiter and 1 overt hypothyroid had nodular colloid goiter. One hyperthyroid patient with metabolic syndrome had nodular hyperplasia of thyroid gland.

Discussion

In our study, out of 60 patients of metabolic syndrome, 30 patients (50%) were euthyroid, 13 patients (21.66%) had subclinical hypothyroid and 12 patients (30%) had overt hypothyroid. Five patients (8.33%) of metabolic syndrome had hyperthyroidism. A cross-sectional study from South India by Shantha et al has shown prevalence of subclinical hypothyroidism as 21.9% and overt hypothyroidism in 7.4% cases of metabolic syndrome.

The female-to-male ratio in our study was 2.25:1 in subclinical hypothyroidism and 2:1 in overt hypothyroidism patients. The female-to-male ratio in hypothyroidism ranges from 2:1 to 8:1 in various epidemiological surveys. Some surveys indicate hypothyroidism to be more prevalent in elderly population, reaching as high as 20%. Shrestha et al observed the association of metabolic syndrome in 21, 5 and 6 cases in 48 euthyroid, 24 hyperthyroid and 28 hyporthyroid groups, respectively.

The commonest symptom in hypothyroid patients was lethargy (77.77%). This was consistent with case-control study by Khurram et al in which 67.9% cases had lethargy. In our study too, dry and coarse skin was mentioned by 72.22% of patients like 70-79% cases in another study. Similarly, cold intolerance,

that was found in 89% of patients in one series and 93% of another series, was prevalent in 66.66% of our cases, which is quite comparable to the 58.25% in Watanakunakorn's. Five out of 14 (35.71%) females had menorrhagia as in the study by Khurram et al. In a cohort study by Scott and Mussey, 28 women (56%) complained of menstrual disturbance, with the most common complaint being menorrhagia (occurring in 18 [36%] of the women). Other symptoms like body aches, weight gain, constipation, paresthesia, hair loss were similar to what has been described in various studies.

In our study, 66.66% patients had puffiness of face as compared to 63.3% in the study by Khurram et al, 79% in Lerman's series and 67% in Watanakunakorn's series.

Thyroid was enlarged in 6 hypothyroid patients (33.33%) as compared to 6.6% in the study by Samanta.

The most common symptom in hyperthyroid patients was nervousness (100%), followed by sweating (80%), hypersensitivity to heat (80%), palpitation (80%), weight loss (60%), fatigue (60%), hyperdefecation (40%) and goiter (60%), which was statistically comparable with the study by Trivalle et al.

Out of 12 patients who underwent FNAC of thyroid, 8 patients (66.66%) had normal cytological findings. Two (1 subclinical and 1 overt) hypothyroid patients had simple colloid goiter and 1 overt hypothyroid patients had nodular colloid goiter. One hyperthyroid patient with metabolic syndrome had nodular hyperplasia of thyroid gland.

In this study, we found that out of 60 patients of metabolic syndrome, 24 (40%) were male and 36 (60%) were female. Male-to-female ratio was 2:3 proving that disease was more dominant in females. Most of the patients of metabolic syndrome were belonging to age group 40-60 years. Mean age of males was 49.6 ± 8.0 years and mean age of female patients was 46.2 ± 7.1 years. Mean age of patients with metabolic syndrome in a study by Bacon and colleagues was 47 years and similarly another study also noted mean age of 54 years. About 23.3% of the patients met all the five diagnostic components of metabolic syndrome. Waist circumference was elevated in almost all (80%) the cases. Other components of metabolic syndrome were distributed in 50-70% of the patients.

Majority of male patients (45%) had waist circumference in range of 90-100 cm. Mean waist circumference of males was 97.9 ± 7.2 cm. Most of the female patients (40%) also had waist circumference in 90-100 cm range. Mean waist circumference of female patients was 97.8 ± 2.1 cm. In previous studies, mean waist circumference of males and females was 102 cm and 92 cm, respectively. About 62% of the patients had triglyceride level between 150 and 174 mg%. Only 14.3% had elevated triglyceride level more than 200 mg%. Mean triglyceride level of males was 160.1 ± 22.6 mg%. Mean level of triglyceride in females was 162.7 ± 27.2 mg%. Liese et al noted hypertriglyceridemia in 50% of the cases. In previous studies, it was observed that mean triglyceride level in the patients of metabolic syndrome was 191.8 mg%.

About half of the patients (50.0%) had HDL level between 30 and 39 mg/dL. Mean HDL level of males was 40.8 ± 6.4 mg/dL. Female patients had mean HDL level 43.4 ± 7.5 mg/dL. There was a significant variation in mean HDL level between male and female patients. Similar studies in the past observed HDL abnormalities in 63.5% of the patients.

In our study, 40% patients of metabolic syndrome were diabetic. Only 8.3% patients had blood sugar in impaired glucose tolerance (IGT) range, 16.6% patients were newly diagnosed diabetics. Maximum number of patients (41.7%) were diabetic for duration more than 10 years. Matteoni et al also performed a similar study and found diabetes mellitus in 23% of cases.

In our study, 53% of patients with metabolic syndrome were hypertensive. In all, 25% were newly diagnosed hypertensives. About 37.5% had hypertension for duration more the 10 years. Kaplan and colleagues noted prevalence of hypertension in 58% patients of metabolic syndrome.

Conclusion

The present study concludes that 50% metabolic syndrome patients had thyroid dysfunction. Subclinical hypothyroidism was present in 21.66% and overt hypothyroidism 20% patients. Hyperthyroidism was observed in 8.33% of metabolic syndrome patients.

The most common symptom in metabolic syndrome patients with hypothyroidism was lethargy/sleepiness followed by dry and coarse skin.

The most common symptom in hyperthyroid metabolic syndrome patients was nervousness (100%) followed by sweating, heat intolerance and palpitation (80%). Thyroid dysfunction patients with metabolic syndrome presenting with goiter underwent FNAC of thyroid - 8 patients (66.66%) had normal cytological findings. Two (1 subclinical and 1 overt) hypothyroid patients had simple colloid goiter and

1 overt hypothyroid patient had nodular colloid goiter. One hyperthyroid patient with metabolic syndrome had nodular hyperplasia of thyroid gland. Metabolic syndrome and thyroid dysfunction are independent risk factors for cardiovascular disease. Their co-existence may even compound the risk of cardiovascular events. Hence, it is worthwhile to screen metabolic syndrome patients for thyroid dysfunction at the earliest for further decrease in cardiovascular events.

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CLINICAL STUDY

One-Step versus Two-Step Diagnostic Test for Gestational Diabetes Mellitus

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ABSTRACT

Aim: Comparison between one-step Diabetes in Pregnancy Study Group India (DIPSI) and American Diabetes Association (ADA) recommended two-step oral glucose tolerance test (OGTT). **Material and methods:** This study has a sample size of 200; 100 participants each were subjected to either of the two tests. Gestational diabetes mellitus (GDM) and non-GDM diagnosed by one-step test versus two-step test, respectively, were compared to one another and results were compared on the basis of various antenatal complications and fetomaternal outcomes. **Results:** No statistical difference was found between both the groups on the basis of various antenatal and fetomaternal outcomes. **Conclusion:** In Indian subcontinent with poor resources and lack of follow-up, single-step DIPSI can be preferred to ADA recommended two-step OGTT; however, large database studies are still required.

Keywords: Gestational diabetes mellitus, Diabetes in Pregnancy Study Group India, one-step test, two-step oral glucose tolerance test

Introduction

Diabetes mellitus is a disorder of carbohydrate metabolism. Diabetes complicating pregnancy has become more common worldwide. Gestational diabetes mellitus (GDM) refers to carbohydrate intolerance that is recognized or develops during pregnancy, irrespective of the treatment with diet or insulin. Women with a history of GDM have a higher risk of future diabetes, particularly type 2 diabetes, and the same holds true for their children.[1] Besides, any glucose intolerance in pregnant women without GDM has been linked with escalated adverse maternal and fetal outcomes. Thus, GDM should be considered as a key opportunity to develop, test and implement clinical strategies for the prevention of diabetes. Action taken at the right time to screen all pregnant women for glucose intolerance, achieve euglycemia and ensure adequate nutrition could help prevent the vicious cycle of passing on glucose intolerance from one generation to another. In the Indian context, screening for diabetes becomes all the more crucial during pregnancy as Indian women have an 11-fold increased risk of developing glucose intolerance during pregnancy compared to Caucasian women.[2]

The world prevalence of diabetes among adults was around 6.4% in 2010, affecting 285 million adults and is estimated to increase up to 7.7% and 439 million adults by 2030. Abnormal maternal glucose regulation has been noted in nearly 3-10% of pregnancies.

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Routine screening is required in the Indian subcontinent because of multifactorial pathology predisposing women to this pregnancy associated comorbidity, the associated risk factors and long-term side effects. Also to mention, the low-cost of screening in a country like India with limited resource availability.

The American College of Obstetricians and Gynecologists (ACOG) recommends universal screening for GDM with a 50 g 1 hour loading test at 24-28 weeks followed by 100 g, 3-hour oral glucose tolerance test (OGTT) for diagnosis. In this approach, a 50 g glucose challenge test, or the O'Sullivan test, is first performed which, if positive, is followed by an OGTT.[3]

After the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, the World Health Organization (WHO) validated Diabetes in Pregnancy Study Group India (DIPSI) as a single step procedure in screening GDM. In the antenatal clinic, after preliminary examination, the pregnant women will be given 75 g glucose load orally, irrespective of her fasting status or timing of previous meal. GDM is diagnosed, if post 2-hour blood glucose value is found to be ≥140 mg/dL.[4-6] This single step procedure has been approved by the Ministry of Health, Govt. of India and also recommended by the WHO.

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010 recommended new terminology and diagnostic cut offs for GDM based on the hyperglycemia and pregnancy outcome study. According to IADPSG guidelines, diabetes first recognized in pregnancy can be classified as gestational or overt. The criteria for diagnosing include:

- Fasting plasma glucose (FPG) ≥126 mg/dL
- Glycated hemoglobin (HbA1c) ≥6.5%
- Random plasma glucose >200 mg/dL.

Successful screening test requires that the condition should be prevalent in the target population (which diabetes is, in Indian subcontinent), screening improves the prognosis and available treatment is effective. There have been several screening guidelines based on the suitability of the test to the population characteristics, cost and screening accuracy. Numerous controversies still exist regarding the test to be used and when the screening strategy should be applied. Factors like clinical judgment and available resources have a key role in choosing the best possible mode for evaluation of GDM, the different screening and diagnostic practices for GDM, and in finally outlining the best suitable option for our economy and population. With so many routine screening options available for GDM, it becomes a challenge in itself for Indian obstetrics to choose the most suited testing method appropriate for a limited resource and poor follow-up economy like ours. Thus, this study was undertaken.

Material and Methods

Source of Data

It was a hospital-based study. All pregnant women in second trimester between 24 and 28 weeks of gestational age, who attend antenatal clinic at Shri Ram Murti Smarak Institute of Medical Sciences (SRMS-IMS), Bareilly, Uttar Pradesh, in a time of 2 years were enrolled in this study after providing informed consent.

Inclusion Criteria

- All consenting pregnant women in second trimester between 24 and 28 weeks who attended antenatal clinic at SRMS-IMS, Bareilly, Uttar Pradesh.
- Pregnant women of any parity.
- Singleton pregnancy.

Exclusion Criteria

- Pregestational diabetes.
- Chronic diseases/cardiac/hepatic/respiratory diseases/any other medical or surgical diseases.
- Taking drugs that alter glucose metabolism.
- Patients who refuse to participate.

Method of Collection of Data

Study design: A clinical study.

Sample size: Two hundred consecutive pregnant women between 24 and 28 weeks of gestational age who attended antenatal clinic of SRMS-IMS, Bareilly, Uttar Pradesh, over a time period of 2 years were included in the study after providing informed consent and were randomized into two groups having 100 patients in each group.

Sample: It is a hospital-based study.

Place: SRMS-IMS, Bareilly, Uttar Pradesh.

Duration: Two years; from October 2017 to November 2019.

Method:

- A hospital-based clinical study designed to compare one-step versus two-step screening test for GDM. A detailed clinical assessment of patient was performed in the outpatient department (OPD),

including history (family history of diabetes, history of previous pregnancies and socioeconomic status, etc.), general physical examination and obstetric examination. Routine investigations during antenatal visits were done. Informed consent of participation was taken during this initial assessment.

- A standard form was used to record the date of the tests performed, detailed clinical assessment of patient, including history and examination findings, investigations, including the test results.

Cut-off values of one-step procedure in screening of GDM:[5,6]

Criteria for Positive Screening of GDM	
DIPSI criteria for screening GDM	2-hour PPBS
Nonfasting OGTT with 75 g glucose	>140 mg/dL

The American Diabetes Association (ADA) recommends, in a two-step procedure, an initial screening by measuring plasma glucose 1 hour after 50 g oral glucose challenge test (OGCT). Those found to be positive at the screening test undergo 100 g OGTT.

ADA Criteria for Diagnosis of GDM	
100 g OGTT	**Cut-off values**
Fasting	95 mg/dL (5.3 mmol/L)
1 hour	180 mg/dL (10 mmol/L)
2-hour	155 mg/dL (8.6 mmol/L)
3-hour	140 mg/dL (7.8 mmol/L)

Two or more of the venous plasma concentrations must be met or must exceed the above values for a positive diagnosis.

Patients who had a positive outcome to either of the screening tests were followed up in high-risk antenatal clinic. Outcome was noted during antenatal period, and as type of delivery, mode of delivery and postpartum events. Fetal outcome was observed. Under high-risk antenatal clinic, they were called for a follow-up fortnightly from 28 to 32 weeks, and weekly thereafter. Standard management protocol for GDM was followed in patients screening positive by one-step or two-step technique. Patients in whom the screening test came out negative were followed-up in regular antenatal clinic.

Observations and Results

This clinical study was conducted in the Dept. of Obstetrics and Gynecology, SRMS-IMS, Bareilly, Uttar Pradesh, India.

The aim of this study was to compare one-step versus two-step diagnostic test for GDM on the basis of various maternal, intrapartum and fetal parameters. A total of 200 antenatal women were recruited in this study; 100 women in each group.

The fetal, maternal and intrapartum outcomes of GDM patients and non-GDM patients of Group A and Group B were compared.

Out of 100 patients in Group A, 12 were found to have GDM by DIPSI criterion and rest 88 were taken as controls (Table 1). In Group B, 10 had GDM and rest 90 were taken as controls (Table 1). In our study, we found that the mean age of patients in Group A was 24.77 years and in Group B was 24.75 years. While comparing parity, as shown in Table 2, 39% and 37% patients in Group A and Group B were primigravidas, and 30% and 37% in Group A and Group B were second gravidas, respectively. Maximum patients in both the groups were either primi- or second gravidas. The mean body mass index (BMI) in patients of Group A was 21.708 kg/m^2 and in Group B was 21.018 kg/m^2. Maximum patients in both the groups had a BMI in the range of 20-25 kg/m^2 (Table 2).

While comparing genitourinary infections, the occurrence rate was 11.36% in non-GDM patients in Group A compared to 7.77% in Group B in the given antenatal period. On the contrary, 33.33% in patients with GDM in Group A and 20% patients with GDM in Group B were found to have genitourinary tract infections (Tables 3 and 4).

About 9.09% non-GDM patients in Group A and 8.88% non-GDM patients in Group B had gestational hypertension as an antenatal complication. Twenty-five percent of GDM patients in Group A and 30% of GDM patients in Group B had gestational hypertension as an antenatal complication (Tables 3 and 4).

About 10.22% of non-GDM patients in Group A and 6.66% of non-GDM patients in Group B had pre-eclampsia as an antenatal complication; 33.33% GDM patients in Group A and 30% patients in Group B had pre-eclampsia as an antenatal complication (Tables 3 and 4).

Table 1. Case Distribution

Case distribution	DIPSI (Group A)	GTT (Group B)	P value
GDM	12	10	0.651
Non-GDM	88	90	
Total	**100**	**100**	

Table 2. Demographic Features

Demographic feature	Group A	Group B
Mean age	24.77	24.75
Mean BMI	21.708	21.018
Parity	P1-P2	P1-P2

Table 3. Maternal Complications in GDM Patients

Maternal complications	GDM (Group A)	GDM (Group B)	P value
Genitourinary infections	4 (33%)	2 (20%)	0.348
Gestational hypertension	3 (25%)	3 (30%)	1
Pre-eclampsia	4 (33.33%)	3 (30%)	1
PROM	4 (33.33%)	2 (20%)	0.646
Preterm delivery	3 (25%)	2 (20%)	1

Table 4. Maternal Complications in Non-GDM Patients

Maternal complications	Non-GDM (Group A)	Non-GDM (Group B)	P value
Genitourinary infections	10 (11.36%)	7 (7.77%)	0.416
Gestational hypertension	8 (9.09%)	8 (8.88%)	0.962
Pre-eclampsia	9 (10.22%)	6 (6.66%)	0.393
PROM	5 (5.68%)	6 (6.66%)	0.785
Preterm delivery	6 (6.81%)	6 (6.66%)	0.968

About 5.68% non-GDM patients in Group A and 6.66% non-GDM patients in Group B had premature rupture of membrane (PROM) complicated pregnancies; 33.33% GDM patients in Group A and 20% GDM patients in Group B had PROM as an antenatal complication (Tables 3 and 4).

About 6.81% non-GDM patients of Group A and 6.66% non-GDM patients of Group B had premature deliveries (<37 weeks). Twenty-five percent of GDM patients in Group A and 20% of GDM patients in Group B had premature deliveries (<37 weeks) (Tables 3 and 4).

Around 5.81% non-GDM patients in Group A had preterm vaginal delivery, 68.60% had full-term vaginal delivery and 25.58% had cesarean section (Table 5). None of the patients underwent instrumental delivery. In Group B, 4.59% non-GDM patients underwent preterm vaginal delivery, 67.81% had full-term vaginal delivery and 27.58% patients had cesarean section. None in Group B also underwent instrumental delivery; 2 stillborn deliveries in Group A and 3 stillborn deliveries in Group B were excluded from the above distribution.

Ten percent GDM patients in Group A and 11.11% GDM patients in Group B had preterm vaginal deliveries. Forty percent GDM patients in Group A and 44.44% GDM patients in Group B had full-term vaginal delivery. None of the patients in both the groups had instrumental delivery. Fifty percent in Group A and 44.44% in Group B had cesarean section, respectively. Two patients from Group A and 1 from Group B were excluded from the above case distribution as they had stillborn delivery (Table 6).

Two non-GDM patients of Group A and 3 non-GDM patients in Group B had intrauterine fetal demise or stillborn deliveries. Two out of 12 GDM patients of Group A and 1 out of 10 GDM patients of Group B had stillborn deliveries or intrauterine fetal demise (Tables 7 and 8). None of the non-GDM patients in both the groups had shoulder dystocia during delivery. One out of 12 GDM patients in the Group A and none of the GDM patients in the Group B had shoulder dystocia during delivery (Tables 7 and 8).

None of the non-GDM patients in Group A had fetal malformations, whereas 2 out of 90 in the non-GDM patients of Group B had this complication. One neonate born to GDM mother in Group A had congenital malformation at the time of birth. However, none of the neonates born to GDM mothers in the Group B had this complication (Tables 7 and 8). About 3.40% neonates of non-GDM women in Group A and 3.33% neonates of

Table 5. Mode of Delivery in Non-GDM Patients

Mode of delivery	Non-GDM (Group A)	Non-GDM (Group B)	P value
Preterm vaginal delivery	5 (5.81%)	4 (4.59%)	0.908
Full-term vaginal delivery	59 (68.60%)	59 (67.81%)	
Instrumental delivery	0 (0)	0 (0)	
Cesarean section	22 (25.58%)	24 (27.58%)	
Total	**86 (100%) + 2 (Stillborn)**	**87 (100%) + 3 (Stillborn)**	

Table 6. Mode of Delivery in GDM Patients

Mode of delivery	GDM (Group A)	GDM (Group B)	P value
Preterm vaginal delivery	1 (10%) + 2 (Stillborn)	1 (11.11%) +1 (Stillborn)	0.971
Full-term vaginal delivery	4 (40%)	4 (44.44%)	
Instrumental delivery	0 (0)	0 (0)	
Cesarean section	5 (50%)	4 (44.44%)	
Total	**10 (100%) + 2 (Stillborn)**	**9 (100%) +1 (Stillborn)**	

Table 7. Fetal Complications in GDM Patients

Fetal complications	GDM (Group A)	GDM (Group B)	P value
Stillborn	2 (16.66%)	1 (10%)	1
Shoulder dystocia	1 (8.33%)	0	1
Fetal malformations	1 (8.33%)	0	1
Respiratory distress	2 (16.66%)	2 (20%)	1
NICU admission	5 (41.66%)	4 (40%)	1

Table 8. Fetal Complications in Non-GDM Patients

Fetal complications	Non-GDM (Group A)	Non-GDM (Group B)	P value
Stillborn	2 (2.27%)	3 (3.33%)	1
Shoulder dystocia	0	0	1
Fetal malformations	0	2 (2.22%)	0.497
Respiratory distress	3 (3.40%)	3 (3.33%)	1
NICU admission	4 (4.54%)	7 (7.77%)	0.371

non-GDM women in Group B had respiratory distress. Two out of 12 GDM patients in Group A and 2 out of 10 GDM patients in Group B had neonates with respiratory distress (Tables 7 and 8). About 4.54% infants of non-GDM patients in Group A and 7.77% infants of non-GDM patients in Group B had neonatal intensive care unit (NICU) admission after delivery (Table 8).

Discussion

Gestational diabetes mellitus refers to any degree of glucose intolerance which arises or is recognized for the first time during pregnancy. It may or may not undergo remission after the end of pregnancy. In comparison with European women, GDM prevalence has increased 11-times in women from the Indian subcontinent.[7] In this study, 100 patients underwent one-step diagnostic test for GDM between 24 and 28 weeks of pregnancy, and same number of comparable antenatal women were subjected to two-step procedure. The diagnostic accuracy appears to be the same by both the tests as the detection rate of GDM was statistically same with insignificant p value between the two groups.

Most of the women recruited in this study belonged to the age group of 21-25 years, thus indicating the increased awareness in the younger population toward antenatal check-ups and hospital delivery. A study done by Qadir et al,[8] had a higher incidence of GDM in higher age group women. In the study done by Priyanka,[9] it was noted that GDM cases belonged mostly to 26-30 years of age group. In our study, the distribution of cases according to parity showed that majority of cases i.e., 39%, were primigravida in Group A and 37% were primigravida in Group B. Only 5% women in Group A and 4% in Group B were of grand multiparity status. This further emphasizes our observation of willingness among young women for routine antenatal check-up, follow-up and institutional/hospital deliveries. We observed that average BMI of GDM patients was 24.70 kg/m^2 in Group A and 24.51 kg/m^2 in Group B. However, a relatively lower mean BMI was observed in non-GDM patients of both the groups - 21.29 kg/m^2 in Group A and 20.63 kg/m^2 in Group B, respectively. The difference in BMI of both the groups was found to be statistically insignificant, but we observed a higher BMI in GDM patients as compared to the non-GDM patients.

In our study, we have compared the various feto-maternal and intrapartum complications of GDM in both the groups by applying different tests. No difference was observed between both the groups on comparing genitourinary complications. It was also noted that the incidence of genitourinary infections was much higher in the GDM when compared to non-GDM patients. In concordance with our study, a study done by Qadir et al also showed that the incidence of recurrent urinary tract infection and vulvovaginal infections in GDM patients is high when compared to non-GDM patients.

The incidence of gestational hypertension was observed to be much higher in GDM patients of Group A, i.e., 25% and of Group B (30%). In the non-GDM patients, the incidence was only 9.09% and 8.88% in both the groups, respectively (p = 0.962). Similar

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findings were noted on comparing the incidence of pre-eclampsia in GDM patients of both the groups with a p value of 1. In a study conducted by Sinha et al,[10] 22% of the DIPSI and 26% OGTT group had hypertensive disorders as comorbidity in their study. Similar to our study, this study also showed no significant difference in both the groups when the parameter hypertensive disorders was compared and an equal predictive value of GDM pregnancies complicated by hypertensive disorders was found by both the tests. Like our study, in the study conducted by Qadir et al, the frequency of hypertensive disorders was higher, though not statistically significant in the GDM patients. Also the parameter PROM was studied in the non-GDM and GDM patients of both the groups. The p value of both the groups in GDM and non-GDM patients was 0.646 and 0.785, respectively, suggesting no statistical difference and the groups to be comparable. Also, the incidence of the parameter was much higher in GDM patients. Similar to our study, a study conducted by Qadir et al also showed higher occurrence of PROM in GDM patients. When the incidence in the GDM and non-GDM patients of both the groups was compared, no statistical difference was observed. However, the incidence of preterm delivery was much higher in GDM group as compared to non-GDM (25% and 20% in GDM patients of Group A and Group B). Saxena et al found an incidence of 12%.[11]

The incidence of normal vaginal deliveries were noted to be lower in GDM patients - 40% in Group A and 44.44% in Group B. None of the patients in both the groups had an instrumental delivery as all the difficult deliveries were mostly subjected to cesarean section in our institute. When the rate of cesarean section was compared, it was found to be twice as much higher in the GDM group as compared to the non-GDM group. Unlike our study, a study conducted by Priyanka stated that 73.33% GDM patients had vaginal deliveries and only 19.44% had cesarean section. Like our study, in the study conducted by Sinha et al, 50% patients diagnosed with GDM by both the tests underwent cesarean and thus the tests were proved to be comparable.

Stillbirth and intrauterine fetal demise are known complications of GDM in the third trimester, as stated in literature. In this study, the incidence of stillborn deliveries in the non-GDM patients was observed to be 2.27% and 3.33% in Group A and Group B, respectively. However, in the GDM patients, the incidence was found to be much higher, 16.66% and 10% in Group A and Group B, respectively. On applying statistical tests, the difference between the two groups in both GDM and non-GDM patients was found to be insignificant. A study conducted by Priyanka, showed that GDM complicated pregnancies had live birth rate of 87.22% and intrauterine death was noted in 7.22% women. On studying the case distribution of shoulder dystocia in non-GDM and GDM patients of both the groups, none of the non-GDM patients had this complication during delivery; however, in GDM complicated pregnancies, 1 patient in Group A and none in the Group B had shoulder dystocia.

In our study, 2 out of 90 non-GDM patients in Group B and none in Group A had fetal malformations. In GDM pregnancies, the incidence rate of 8.33% was noted for the complication in Group A. However, none of the GDM pregnancies diagnosed by two-step test had fetal malformations. The study group was thought to be too small to draw a comparison between the GDM and non-GDM patients in regard to this parameter. On applying statistical tests, the value was found to be insignificant but not much relevant and the two groups were comparable. Sinha et al also found similar results.

On comparing the incidence of respiratory distress in infants of non-GDM group, it was found to be only 3.40% and 3.33% in Group A and Group B, respectively; however, diabetes complicated pregnancies had a much higher incidence of 16.66% and 20% in Group A and Group B. Lastly, on comparing the incidence of NICU admission in the two groups, 4.54% and 7.77% babies born to non-GDM mothers were admitted to NICU in Group A and Group B, respectively, immediately after birth. However, a very high incidence was observed in the babies of GDM mothers, i.e., 41.66% and 40% in Group A and Group B (p = 1). Like our study, in the study done by Sinha et al, 31% cases of DIPSI group and 45.50% cases of GTT group developed respiratory distress. Difference between the two was not statistically significant.

In this study, we have compared various complications of GDM in both the groups and we observed no statistical difference. Also, no difference exits in the diagnostic accuracy of both the tests. Similar to our study, the study conducted by Sinha et al also observed no statistical difference between one-step and two-step procedure in respect to various maternal and fetal outcomes.

Conclusion

The incidence of GDM in this study was found to be 12% by one-step and 10% by two-step procedure. The

high pick up rate was attributed to our institute being a tertiary care center with maximum cases of complicated pregnancy. The statistical difference between both the groups in regard to all the parameters studied was found to be insignificant.

Hence, we state that one-step test, which is more feasible, economical and applicable in population of India, may help in fighting to diagnose GDM, reducing feto-maternal morbidity associated with it, in comparison to a more cumbersome and robust two-step diagnostic test recommended by the ACOG.

In our study, we compared and studied the statistical difference of various maternal, fetal and intrapartum complications among two different groups. No statistical difference was observed between all the parameters assessed in this study.

Thus, we conclude that both the tests not only have an equal predictive rate for various complications but also equally effective in diagnosing GDM. Timely diagnosis and management of GDM will prevent diabetes in future life. If adequate obstetric care is provided to the antenatal patients with GDM, many maternal, fetal and intrapartum complications can be markedly reduced, especially in low resource countries like India.

Thus, we suggest that ACOG recommended two-step test, which is less feasible and applicable in Indian population can be safely replaced by one-step diagnostic test. However, to state such a fact, large scale studies, exhaustive follow-up and meta-analysis is required. For us, as clinicians, it's our role to fight against all odds in converting the Diabetes Capital of the World to a well-controlled diabetic country.

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ORIGINAL STUDY

Hypothyroidism in Metabolic Syndrome

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ABSTRACT

Background: Metabolic syndrome (Syndrome X/Insulin resistance syndrome) consists of central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycemia and hypertension as its major features. All of them can be influenced by the functioning of a 20 g endocrine organ, the thyroid gland. **Aims and objectives:** To study the proposed association between metabolic syndrome and thyroid dysfunction. **Material and methods:** Hundred subjects aged more than 18 years, willing to participate in the study and fulfilling criteria of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) for diagnosis of metabolic syndrome were included. Detailed clinical examination and laboratory investigations of all subjects were done. Risk factors were identified and analyzed by comparing the subjects with and without thyroid dysfunction. **Results:** Eighty-one out of 100 subjects with metabolic syndrome belonged to the age group between 41 and 70 years. Females comprised 60% of the total patient population with sedentary lifestyle as the major risk factor, whereas males comprising rest of the 40% had addictive behaviors as major risk factors. Observation of individual parameters under NCEP-ATP III showed that 57 patients fulfilled all 5 criteria, 34 patients fulfilled 4 and 9 patients fulfilled 3 criteria. Obesity and dyslipidemia were common among female subjects, whereas impaired glucose tolerance and hypertension were common among males. Thyroid dysfunction in the form of hypothyroidism was present in 30 subjects with females (23 patients) being the statistically significant population ($p < 0.0001$). Hypothyroidism was of subclinical type in 21 of these 30 subjects. None had hyperthyroidism. Left ventricular ejection fraction (mean ± SD) was lowered to 42.67 ± 6.53 from 49.07 ± 7.48 in presence of thyroid dysfunction in these subjects with metabolic syndrome ($p < 0.0001$). **Conclusion:** Metabolic syndrome and hypothyroidism (even subclinical) are both individual as well as combined risk factors for development of atherogenic dyslipidemia, diabetes mellitus and cardiovascular disease with elderly females comprising the high risk group.

Keywords: Metabolic syndrome, thyroid dysfunction, hypothyroidism

Introduction

Prevalence of both metabolic syndrome and thyroid dysfunction depend on features like age, sex, ethnicity and geographic factors.[1] With increasing global industrialization and rising rates of obesity, prevalence of metabolic syndrome is expected to increase.

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Metabolic syndrome and hypothyroidism share insulin resistance as the common pathophysiologic mechanism manifesting as obesity, dyslipidemia and hypertension.[2,3] Study of association between these two disorders will help early identification of at risk group and initiation of treatment for thyroid dysfunction in individuals with metabolic syndrome.

Material and Methods

This was an observational and noninterventional study conducted in our Government Medical College and attached tertiary care hospital.

Study Group

Inclusion Criteria

Total of 100 subjects aged more than 18 years, willing to participate in the study and fulfilling criteria of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) for diagnosis of metabolic syndrome were included (Table 1).

Exclusion Criteria

- Patients already diagnosed with thyroid dysfunction, thyroid malignancy.
- Pregnant females.
- Patients receiving drugs interfering with thyroid function.

Methods

- Detailed history of the patient including symptoms, past illness, occupation, lifestyle, familial and other comorbid illness obtained.
- General and systemic clinical examination of the patient was performed. Waist circumference and blood pressure (BP) were recorded.
- Following investigations were carried out:
  - Serum fasting lipid profile
  - Fasting blood sugar (FBS), postprandial blood sugar (PPBS), A_{1C}
  - Thyroid function tests - Serum thyroid-stimulating hormone (TSH), free T3, free T4 (Table 2)
  - Complete blood count
  - Renal and liver function tests
  - Urine analysis
  - 2D ECHO
  - Chest radiograph
  - Ultrasonography abdomen with kidney, ureter and bladder
  - Electrocardiograph
  - Fundus examination.
- Statistical analysis done for better understanding and to provide logical support to results.

Results

Patient population was largely comprised of middle-aged individuals with 81 out of 100 subjects with metabolic syndrome belonging to the age group between 41 and 70 years. Females comprised 60% of the total patient population with sedentary lifestyle as the major risk factor, whereas males comprising rest of the 40% had addictive behaviors as major risk factors (Table 3). Observation of individual parameters under NCEP-ATP III showed that 57 patients fulfilled all 5 criteria, 34 patients fulfilled 4 and 9 patients fulfilled 3 criteria. Sixty-six patients had waist circumference that satisfied the criteria for metabolic syndrome, whereas 73 patients had body mass index (BMI) of >25 kg/m^2.

Tables 1. Clinical Identification of the Metabolic Syndrome: Any Three of the Following (NCEP-ATP III Criteria)[4]

Risk factor	Defining level
Abdominal obesity	Waist circumference
Men	>102 cm
Women	>88 cm
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL

Table 2. Thyroid Function Tests - Reference Values

Thyroid status	Serum TSH (μIU/mL)	Serum free T4 (ng/dL)
Eu	0.27-4.2	0.93-1.7
SCH	4.3-10	0.93-1.7
OH	>10	<0.93

Eu = Euthyroidism; SCH = Subclinical hypothyroidism; OH = Overt hypothyroidism.

Table 3. Parameters of the Study Population

Parameters	Results
Age (years)	57.63 ± 10.58
Sex (M:F)	40:60
Waist circumference (cm)	
Men	101.43 ± 7.93
Women	89.93 ± 9.04
Blood pressure (mmHg)	146.06/90.4
Fasting glucose (mg/dL)	133.71 ± 26.21
Total cholesterol (mg/dL)	233.45 ± 49.76
Serum triglycerides (mg/dL)	167.43 ± 20.53
Serum HDL (mg/dL)	
Men	37.18 ± 8.10
Women	39.18 ± 7

Table 4. Association of Components of Metabolic Syndrome with Thyroid Function

Thyroid status	Waist circumference (cm)	Blood pressure (mmHg)	Fasting glucose (mg/dL)	Serum Triglycerides (mg/dL)	Serum HDL (mg/dL)	Total cholesterol (mg/dL)
Eu	95.91	142.8/84.3	123.36	161.97	39.16	214.03
SCH	91.67	146.6/88.6	130.38	172.29	37.33	262.67
OH	91.14	150.4/94.8	144.22	198.56	34.78	316.86

Table 5. Comparison of Parameters of Metabolic Syndrome with Thyroid Dysfunction Between Genders

Parameters	Male (Mean ± SD)	Female (Mean ± SD)
Waist circumference (cm)	91.58 ± 7.75	101.60 ± 7.84
Blood pressure (mmHg)	145.5/90.9 (mean)	148.4/91.7 (mean)
Fasting glucose (mg/dL)	132.69 ± 27.12	135.4 ± 24.98
Serum triglycerides (mg/dL)	167.60 ± 22.02	167.18 ± 18.32
Serum HDL (mg/dL)	39.33 ± 6.89	37.2 ± 8.86
Total cholesterol (mg/dL)	240.22 ± 45.66	226.55 ± 59.19
Serum TSH (μIU/mL)	7.62 ± 8.36	4.95 ± 3.64
Serum free T4 (ng/dL)	1.08 ± 0.26	1.16 ± 0.24

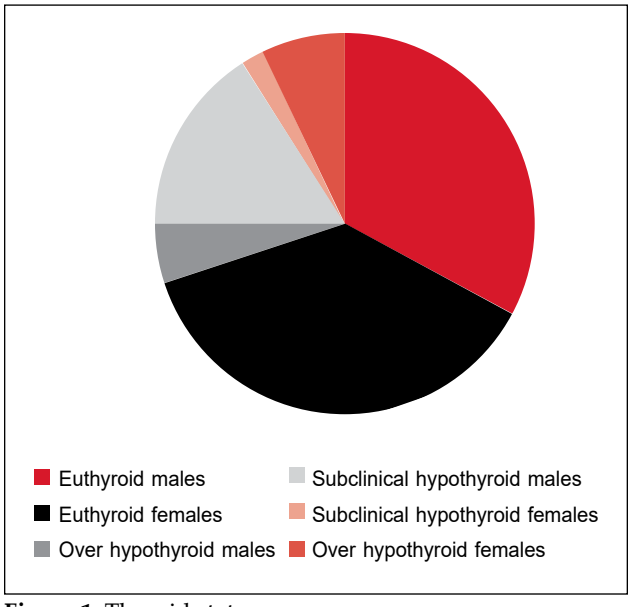

Figure 1. Thyroid status.

Sixty-six patients had hypertension and 33 had prehypertension. Only three patients were normotensive. Fifty patients had FBS between 100 and 125 mg/dL and 39 patients had frank type 2 diabetes. Eighty patients had triglyceride (TG) values >150 mg/dL and 4 among them had values >200 mg/dL. Thirty-one (78%) males had high-density lipoprotein (HDL) of <40 mg/dL and 56 (93%) females had HDL of <50 mg/dL. Total cholesterol and low-density lipoprotein (LDL) (not included in definition of metabolic syndrome) too were elevated among these patients. Obesity and dyslipidemia were common among female subjects attributable to sedentary lifestyle, whereas impaired glucose tolerance and hypertension were common among male subjects attributable to presence of addicting habits. Incidence of thyroid dysfunction was more common in patients satisfying more than three criteria for metabolic syndrome, in women with waist circumference >88 cm and in patients with diabetes mellitus (Table 4).

Prevalence of thyroid dysfunction in the form of hypothyroidism was statistically significant ($p < 0.0001$) in females than in males with 23 out of 60 female and only 7 out of 40 male subjects diagnosed with hypothyroidism (Table 5 and Fig. 1). Hypothyroidism was of subclinical type in 21 (16 females and 5 males) out of these 30 patients. None had hyperthyroidism. Left ventricular ejection fraction (LVEF) (mean ± SD) was lowered to 42.67 ± 6.53 from 49.07 ± 7.48 in presence of thyroid dysfunction in these subjects with metabolic syndrome ($p < 0.0001$).

Discussion

Metabolic syndrome is a cluster of cardiometabolic risk factors and hypothyroidism is an independent risk factor for cardiovascular disease.[5-9] Both share insulin resistance as the central pathophysiologic mechanism. Insulin resistance favors lipolysis causing development of dyslipidemia and impaired glucose tolerance.[10]

Abdominal obesity further increases insulin resistance by producing inflammatory cytokines like tumor necrosis factor-ά (TNF-ά) and interleukin-6 (IL-6).[11]

Adiponectin released by adipose tissue enhances the action of insulin, but is deficient in obese persons.[12,13] BMI >25 kg/m^2 definitely forms a risk factor for atherogenic dyslipidemia and insulin resistance.[14,15] Patients not having frank diabetes at present are prone to develop it in the future. Atherogenic dyslipidemia is reflected in the form of high serum TG, total cholesterol, LDL and low HDL. Studies suggest presence of linear correlation between dyslipidemia (high serum TG and cholesterol) and serum TSH values.[16,17] Thyroid hormone affects tissue thermogenesis, erythropoiesis, lipid metabolism, systemic vascular resistance, blood volume, cardiac contractility, heart rate and cardiac output. Any thyroid dysfunction, therefore, alters cardiovascular dynamics significantly. Cardiac output increases 50-300% higher than in normal individuals in hyperthyroidism, whereas it may decrease by 30-50% in hypothyroidism. However, restoration of normal cardiovascular hemodynamics is possible with treatment of thyroid dysfunction.[6-8]

Present study reiterates that metabolic syndrome and hypothyroidism are both individual as well as combined risk factors for development of disease processes like cardiovascular disease and diabetes mellitus with elderly females comprising the high risk group.

Conclusion

Patients with metabolic syndrome and hypothyroidism (even subclinical) are prone to atherogenic dyslipidemia and cardiovascular events. Early thyroxine replacement can prevent cardiovascular events in these patients. Hence, we recommend routine screening for thyroid dysfunction in females with metabolic syndrome. However, theoretical benefits of thyroxine replacement in subclinical hypothyroidism is to be confirmed by future randomized trials.

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CASE REPORT

Is It Structural or Metabolic? A Diagnostic Dilemma

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A B S T R A C T

Osmotic demyelination syndrome (ODS), a disease affecting chronic alcoholic and malnourished patients was described by Adams and colleagues in 1959. It is also known as pontine myelinolysis. Pontine myelinolysis can be subdivided into central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) depending upon the level of demyelination, within the pons or outside the pons, respectively. Rapid correction of hyponatremia contributes to the pathogenesis of ODS. Whenever a chronic alcoholic and/or malnourished develops confusion, quadriplegia, pseudobulbar palsy and pseudocoma (Locked-in-syndrome) over a period of several days, a high index of suspicion for ODS must be held.

Keywords: Osmotic demyelination syndrome, central pontine myelinolysis, extrapontine myelinolysis, hyponatremia

Introduction

Osmotic demyelination syndrome (ODS), was described by Adams et al in 1959 as a disease affecting alcoholics and malnourished people. The etiology of ODS was not known for a long time but few authors suspected the cause to be either toxin or nutritional deficiency. 'Central pontine' indicates the site of lesion and the term 'myelinolysis' was used to emphasize that myelin was affected preferentially compared to other neuronal elements. Central pontine myelinolysis (CPM) is a noninflammatory, demyelinating condition characterized primarily by the systemic, noninflammatory destruction of myelin sheath in the basis pontis and primarily results from aggressive correction of hyponatremia.

In 1983, Laureno et al suggested rapid correction of hyponatremia as the cause for the condition, based on experimental data on animal model. They suggested that the condition could be prevented by correcting hyponatremia by <10 mmol/L in 24 hours.

Although uncommon, ODS has been reported at a rate of 0.4-0.56% for patients admitted to neurology services and 0.05% of cases admitted in a general hospital. A study found 0.3-1.1% of patients with unsuspected CPM during autopsies, with a greater percentage of CPM noted in patients with liver transplant and chronic liver disease. An autopsy-based study documented a prevalence rate of 0.25-0.5% in the general population and 10% in patients undergoing liver transplantation.

Case Report

A 63-year-old male presented to the emergency department (ED) with an unsteady gait, giddiness and left-sided weakness. His medical history was significant for hypertension, on irregular treatment and history of

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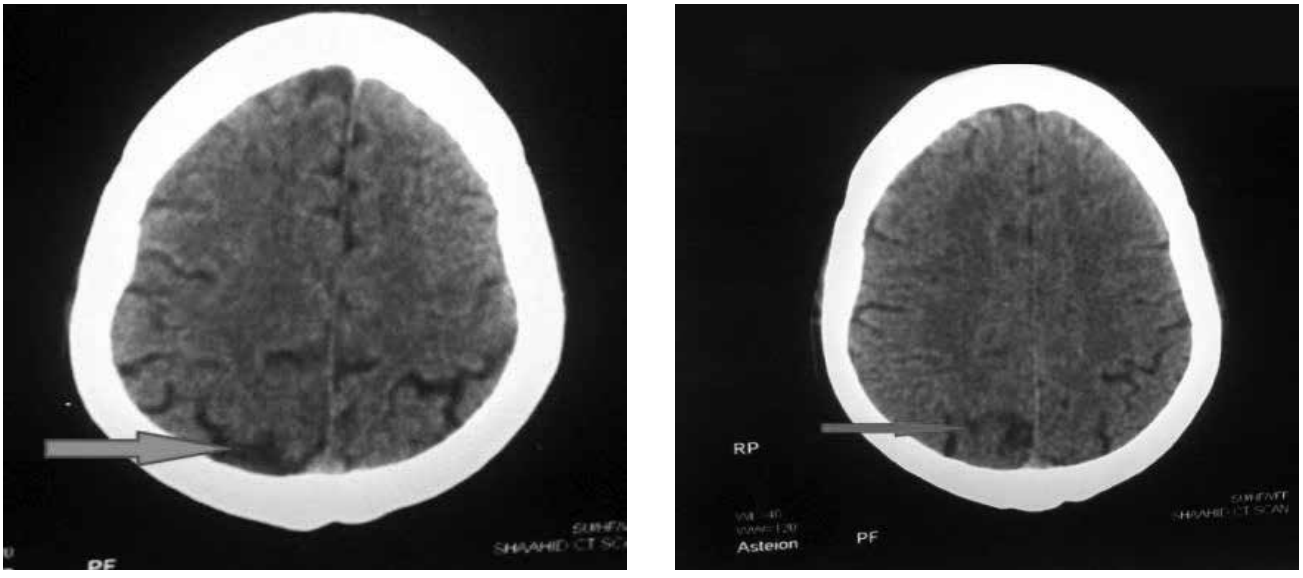

Figure 1. CT brain images showing patchy hypodensity at right posterior parietal cortex (*arrow*).

consumption of alcohol in the past. He had retrospective history of intravenous (IV) fluid infusion at a private hospital 2 hours prior to the initial presentation to ED.

General physical examination was unremarkable. Neurological examination revealed that the patient was alert, oriented with facial deviation towards right side and power was grade 0/5 both in left upper limb (UL) and lower limb (LL) with NIHSS score of 11. Fundus examination was normal. An initial diagnosis of cerebrovascular accident (CVA) left hemiplegia with left upper motor neuron (UMN) facial palsy was made.

Laboratory investigation showed that the patient had significant hypernatremia (149 mmol/L) at the time of presentation. Computed tomography (CT) of the brain (Fig. 1) performed approximately 3 hours after initial presentation was consistent with features of CVA (right parasagittal posterior parietal cortex).

On next day, 16 hours after initial presentation he developed dysarthria, dysphagia and inability to use his right LL. Motor examination showed decreased tone in left UL and LL, power of grade 0/5 in left UL and LL; grade 2/5 in right LL with exaggerated deep tendon reflexes, left equivocal plantar response (NIHSS score of 16). Pupils were pinpointed and sluggishly reacting to light. Ocular fundus examination was normal. Patient was shifted to intensive care unit (ICU) and mechanically ventilated. Provisional diagnosis of probable posterior circulation restroke at the level of pons was made. Laboratory investigations revealed normal cell count and renal parameters. However, repeat sodium level was elevated (146 mmol/L).

Magnetic resonance (MR) (Fig. 2) imaging, performed 36 hours after the initial CT, showed well-defined area of diffusion restriction in the lower central pons bilaterally.

Differential diagnosis of pontine infarct, pontine hemorrhage and ODS was made.

In view of IV fluid infusion prior to presentation to our ED and clinical features of ataxia, quadriparesis, dysphagia, dysarthria without ophthalmoplegia and sensory loss suggestive of ODS with two elevated values of sodium and also classical MRI findings of diffusion restriction in the lower central pons bilaterally, diagnosis of ODS was made and treated accordingly. During the course of hospitalization, patient developed VAP for which he was treated and was discharged 3 weeks after admission with residual minimal left hemiparesis.

Discussion

It is important to differentiate between structural and metabolic causes of neurological deficits, and if structural, the level of lesion has to be localized. Lower cranial nerve palsies and bilateral findings point towards lower pontine lesion, the cause of which may be:

- Pontine infarct
- Pontine hemorrhage
- Osmotic demyelination syndrome (ODS).

Pontine Infarct

Isolated pontine strokes are relatively frequent, but they can occur as part of the posterior circulation infarction.

Ventral infarcts are the most common type of isolated pontine infarction (51-58%).

Anteromedial infarct causes hemiparesis or hemiplegia, contralateral ataxia, dysarthria, dysphagia, nystagmus and often ipsilateral facial palsy. Less frequently associated is contralateral loss of proprioception, paresis of the ipsilateral horizontal gaze and internuclear ophthalmoplegia. Anterolateral infarct may produce hemiparesis, ataxia, loss of position sense and loss of vibration sense. Pure motor stroke, ataxic hemiparesis, dysarthria-clumsy hand or sensorimotor stroke are the other forms of manifestations of the anterolateral strokes.

Dorsolateral pontine strokes may lead to contralateral hemiparesis, ipsilateral facial weakness, ipsilateral loss of facial pain and temperature sensation, hearing loss and ataxia. Rostral dorsolateral pontine infarct can manifest as ipsilateral Horner's syndrome, contralateral ataxia and contralateral loss of body pain and temperature sensation.

Pontine Hemorrhage

Classic clinical presentation of pontine hemorrhage is acute onset of coma, tetraparesis, respiratory failure and oculomotor signs, and most patients have diminished sensorium. Prodromal symptoms, such as headache, nausea and vomiting, respiratory dysfunction and dysarthria may be present.

Osmotic Demyelination Syndrome

ODS is characterized by its subacute sequential presentation, initial encephalopathy or seizures, followed by rapid recovery in relation to electrolyte or osmolality correction, and subsequent clinical deterioration. Clinical manifestations include predominant ataxia (reflecting involvement of pontocerebeller fibers), dysarthria, dysphagia, quadriparesis and alteration in sensorium. Pupillary and oculomotor signs were less frequently noted. Extrapontine extension results in behavioral abnormalities and movement disorders. The transverse pontocerebellar fibers are most frequently involved, followed by rostrocaudal tracts. Tegmentum and corticospinal tracts are usually spared.

Conclusion

Presence of seizures, predominant ataxia, quadriparesis, pupillary and oculomotor signs with hypernatremia and classical MRI findings of bilateral diffusion restriction are noted in ODS. Behavioral and abnormal movements occur if there is an extrapontine extension. Absence of Horner's syndrome, internuclear ophthalmoplegia and sparing of primary and posterior column sensation favors ODS.

Early diagnosis and early differentiation between structural and metabolic cause of neurological deficits will help avoid inadvertent usage of anticoagulants, antiedema measures, repeated imaging (radiation exposure) and stroke resuscitative interventions. Targeted therapy towards the correction of metabolic parameters will lead to a favorable outcome.

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News and Views

Should Combination Therapy be the First-line of Treatment in Type 2 Diabetes?

Combined therapy with sodium-glucose cotransporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1RA), compared to either drug alone, is associated with reduced risk of all-cause mortality and cardiovascular disease (CVD), according to a new study published in the journal *Diabetes, Obesity and Metabolism*.[1]

This study retrospectively analyzed data of people with type 2 diabetes receiving insulin to examine the risk of all-cause mortality, hospitalization and cardiovascular outcomes at 5 years following monotherapy with either SGLT2i or GLP-1RA alone or their combination (SGLT2i + GLP-1RA). Out of the 2.2 million patients included, 143,600 received SGLT2i, 186,841 received GLP-1RA, while 108,504 were treated with the combination. The controls received neither SGLT2i nor GLP-1RA.

The risk of all-cause mortality was found to be decreased in all three intervention groups over a period of 5 years with hazard ratios (HR) of SGLT2i 0.49, GLP-1RA 0.47 and combination 0.25.

Similarly, the risks of hospitalization (HR 0.73, 0.69, 0.60) and myocardial infarction (HR 0.75, 0.70, 0.63) were also reduced in SGLT2i arm, GLP-1RA arm and the combination arm, respectively.

At 5 years, treatment with SGLT2i (vs. controls) reduced the risk of all-cause mortality with HR of 0.49. SGLT2i also reduce the risk of hospitalization (HR 0.73), myocardial infarction (HR 0.75), unstable angina (HR 0.79), heart failure (HR 0.73), atrial fibrillation (HR 0.74), stroke (HR 0.75), peripheral vascular disease or PVD (HR 0.79), lower limb amputation (HR 0.69) and chronic kidney disease or CKD (HR 0.79).

Similar trend was noted with GLP-1RA monotherapy (vs. controls) at 5 years with reduction in the risk of all-cause mortality (HR 0.47), hospitalization (HR 0.69), acute myocardial infarction (HR 0.70), unstable angina (HR 0.73), ischemic heart disease or IHD (HR 0.85), heart failure (HR 0.73), atrial fibrillation (HR 0.77), stroke (HR 0.77), PVD (HR 0.89), lower limb amputation (HR 0.66) and CKD (HR 0.90).

Treatment with combination therapy (SGLT2i + GLP-1RA) also reduced the risk of all-cause mortality (HR 0.25), of hospitalization (HR 0.60), acute myocardial infarction (HR 0.63), unstable angina (HR 0.75), IHD (HR 0.84), heart failure (HR 0.60), atrial fibrillation (HR 0.65), stroke (HR 0.69), PVD (HR 0.84), lower limb amputation (HR 0.59) and CKD (HR 0.72) vs. controls.

This study demonstrates that the risk of all-cause mortality and CVD in patients with type 2 diabetes was reduced in all the three intervention arms when compared to the control group. However, the greatest reduction in risk for all-cause mortality was seen with combination therapy. Similarly, the probability of hospital admission was lowest with combination therapy, which also conferred greater cardiovascular protection. Optimal timely glycemic control prevents or delays the onset of diabetes-related macro- and microvascular complications. The antidiabetic drugs should address the "ominous octet" of factors implicated in pathophysiology of type 2 diabetes. They should also be cardioprotective and renoprotective and not just lower blood glucose. SGLT2i and GLP-1RAs are relatively newer antidiabetic drugs, which have also shown extra-glycemic benefits with improvements in cardiovascular and renal outcomes, besides effective glucose-lowering effects in patients with type 2 diabetes, with cardiovascular risk factors or underlying heart disease. Hence, they are game changers in diabetes care. Their combination might potentially provide superior control of blood glucose with low hypoglycemic risk along with cumulative cardiovascular and renal protection.

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Simple Blood Test for Bipolar Disorder: Study

Researchers at the University of Cambridge created a straightforward blood test to improve the precision of bipolar illness diagnoses, according to a study published in *JAMA Psychiatry*. This test was found to be very helpful when used in conjunction with a digital

mental health assessment. It can identify up to 30% of bipolar individuals with accuracy.

Bipolar disorder and major depressive disorder are diseases that have similar symptoms but require distinct pharmacological treatments; biomarker testing may help physicians differentiate between them.

This study's findings suggest that the blood test can complement existing psychiatric diagnostic methods while shedding light on the biological underpinnings of mental health disorders. Notably, around 1% of the population experiences bipolar disorder, yet nearly 40% of those affected receive a misdiagnosis of major depressive disorder. The researchers utilized samples and data from the Delta study conducted in the UK from 2018 to 2020. The data included information of individuals previously diagnosed with major depressive disorder within the last 5 years, and who were currently displaying depressive symptoms.

The study identified a distinct biomarker signal for bipolar disorder, even after adjusting for confounding factors like medication. The combination of patient-reported information and the biomarker test significantly enhanced diagnostic accuracy for individuals with bipolar disorder, particularly in cases where the diagnosis was less evident.

(Source: https://www.tribuneindia.com/news/health/simple-blood-test-can-help-diagnose-bipolar-disorder-accurately-study-557857)

Study: Extreme Heat Linked to More Cardiovascular Death

A study published in *Circulation* suggests that extreme heat will drive an increase in cardiovascular-related fatalities in the US between 2036 and 2065. The impact of underlying health issues and socioeconomic challenges will be disproportionately felt by vulnerable groups, particularly those 65 years of age and older and persons of color. The study projects an increase in summer days with temperatures reaching at least 90 degrees, as indicated by the heat index, which takes humidity into account. As a result, this tendency is anticipated to change. Although extreme heat currently contributes to less than 1% of cardiovascular deaths, the modeling analysis forecasts a change in this pattern. While most individuals can adapt to extreme heat through mechanisms like perspiration, those with underlying health issues, including diabetes and heart disease, face heightened risks of heart attacks, irregular heart rhythms or strokes.

The study's predictions were generated by evaluating county-level data from 48 states between May and September in the years 2008-2019, during which more than 12 million cardiovascular-related deaths occurred. Environmental modeling estimates indicated that the heat index exceeded 90 degrees approximately 54 times each summer. Researchers linked these extreme temperatures to an average of 1,651 annual cardiovascular deaths nationally. Further modeling analyses, incorporating environmental and population changes, anticipate that between 2036 and 2065, there will be about 71 to 80 days each summer with temperatures feeling 90 degrees or hotter. The general population is expected to experience a 2.6-fold increase in heat-related cardiovascular deaths, requiring minimal greenhouse gas emissions. If these emissions increase and are not controlled, then extreme heat would potentially triple the fatality.

(Source: https://www.daijiworld.com/news/newsDisplay?newsID=1135159)

Research Reveals Mobile Phone Use Linked to Lower Semen Quality

A University of Geneva study published in *Fertility & Sterility* revealed that frequent mobile phone usage can reduce sperm concentration and total count. However, it found no connection between mobile phone use and sperm motility and morphology.

The study analyzed data from 2,886 Swiss men aged 18 to 22 (recruited between 2005 and 2018) and found a significant decrease of 21% in sperm concentration for those who used their phones more than 20 times a day compared to those who used them less than once a week. Sperm quality is evaluated based on parameters including sperm concentration, total count, motility and morphology. Over the past half-century, numerous studies have reported a decline in semen quality, with sperm count dropping from an average of 99 million per milliliter to 47 million per milliliter. This decrease is believed to result from a combination of environmental factors like endocrine disruptors, pesticides and radiation, as well as lifestyle factors such as diet, alcohol consumption, stress and smoking. Notably, the study did not find a correlation between the position of the phone, such as being in a trouser pocket, and lower semen parameters.

(*Source: https://www.daijiworld.com/news/newsDisplay?newsID=1135820*)

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