Pharmacological Considerations in the Interpretation of Biochemical Results in Diabetic Patients with Cardiovascular Complications

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Abstract

Diabetes mellitus with cardiovascular diseases is often a multi-systemic disease that requires a multi-therapeutic approach which mostly poses a challenge to laboratory result interpretation. The non-availability of information on many patients due to poor referral, documentation and record keeping has resulted in isolated interpretation of laboratory result of diabetic patients with multisystemic complications. This has led to both analytical and post-analytical errors which has a negative impact on total quality of results. Therefore, this review showed the possible therapeutic treatment of a diabetic patient with cardiovascular disease and how their pharmacological role could affect laboratory result.

Introduction:

There is a high global prevalence of diabetes mellitus (DM) which increases the likelihood of patients presenting with the disease as a comorbid condition alongside other disease entities, and/or its associated cardiovascular complications. These scenarios may necessitate co-management by different physicians frequently resulting in the use of multiple drugs with little recourse to the implications of these sometimes-unplanned drug combinations on the body's metabolic balance, the resultant biochemical result findings, and their interpretation. Interpretation of these laboratory results without foreknowledge of all the medications the patient had been exposed to is a common occurrence especially in high-pressured healthcare systems due to a tight work schedule amongst other possible reasons. Little attention is usually given to comprehensive information on therapeutics before laboratory testing and biochemical result interpretation. This has contributed significantly to post-analytical error, thereby reducing the overall quality of the biochemical test result. There is a need for more attention to be given to the post-analytical testing phase of the laboratory as is with the pre-analytical and analytical phases because the appropriate interpretation of precise and accurate laboratory data will, to a significant extent, determine the clinical utility of laboratory test results in general, and particularly in diabetes mellitus patients on multiple medications. Thus, if the overall clinical utility of the laboratory test result is to be considered,

the total testing process must be the focus, not just the analytical phase considering its significance.(1) There are 422 million diabetes mellitus (DM) patients worldwide with middle and low-income countries contributing higher to the global prevalence. Over the past few decades, the prevalence of DM has risen significantly in nearly all countries and may be considered a growing epidemic.(2) It is predicted that Africa may have the world's largest surge in non-communicable disease (NCD) deaths over the next decade due to the epidemiological transition of disease.(3) In Nigeria, NCDs account for an annual death of about 36 million with cardiovascular diseases having the highest contribution of about 17.3 million deaths while diabetes mellitus is the commonest cause of cardiovascular diseases.(4) This poses a huge challenge to the health sector including the clinical laboratory. Diabetes mellitus is a multi-systemic disease that requires a multidisciplinary management approach which mostly leads to multiple drug therapy and adversely affects laboratory test results. Therefore, this review emphasizes on the importance of the foreknowledge of the therapeutic profile of diabetes mellitus patients in the total laboratory testing process to ensure the provision of clinically useful laboratory results to patients and their clinicians, thus enhancing the quality of life of diabetes mellitus patients, improving the practice of clinicians, and reducing the overall health cost.

Diabetic Complication and Therapeutics:

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in either insulin secretion, insulin action, or both.(5) Diabetic mellitus patients are prone to acute and chronic complications. Many years of inadequately controlled hyperglycaemia lead to multifarious, primary vascular complications that affect small vessels (microvascular), large vessels (macrovascular), or both. The cardiovascular complication commonly associated with diabetes mellitus is associated with various mechanisms which include glycosylation of intracellular and extracellular proteins and lipid in a maillard reaction leading to the formation of advanced glycation end products, increased superoxide production, activation of Protein kinase C, a signalling molecule that increases vascular permeability and causes endothelial dysfunction, accelerated hexosamine biosynthetic and polyol pathways leading to accumulation of sorbitol within tissues. Moreso, associated hypertension and dyslipidaemias, as well as arterial micro- thromboses, proinflammatory and prothrombotic impact impair vascular autoregulation.(6)

The acute complications of DM include diabetic ketoacidosis, hyperosmolar hyperglycaemic non-ketotic coma, and hypoglycaemia which are caused by an acute increase or decrease of glucose in the bloodstream. On the other hand, the chronic complications may lead to cardiovascular diseases via vascular damage due to chronic hyperglycaemia resulting to microvascular and macrovascular complications. Chronic microvascular complications of diabetes comprise of microvascular diseases which include retinopathy, neuropathy nephropathy, encephalopathy, erectile dysfunction, cardiomyopathy and periodontal disease. Macrovascular complications include diabetic myonecrosis, cardiovascular accident, carotid artery stenosis, diabetic foot ulcer, coronary artery disease and female infertility. Additionally, hyperglycaemia reduces the immune cells function and increases inflammation, predisposing the afflicted persons to respiratory infections such as pneumonia and influenza, wound infections, restrictive lung disease, lipohypertrophy and depression. The implication is that most diabetics are frequently on multiple drug therapy that could lead to mis-interpretation of laboratory results if their drug history is not taken into cognisance [Table 1].

Table 1: Most Frequent Laboratory Changes Upon Cardiovascular Drug Treatment

Dysglycemia due to coadministration of antibiotics with hypoglycaemics
Erroneous eGFR due to positive or negative interference of drugs in serum creatinine estimation which may be in vitro or in vivo
Thiazide induced hyperlipidaemia
Changes in serum calcium due to effect of diuretics-loop diuretic is associated with hypercalcemia on the contrary thiazide diuretic is linked to hypocalcaemia
Electrolyte changes associated with diuretics
Dysglyceamia due to effect of statins, thiazides and beta blockers
Drug-induced azotaemia
Hypervolemic hyponatremia in elderly with a state of endogenous or exogenous active ADH secretion such as chronic renal failure, excessive water intake, low salt intake, heart failure, concurrent analgesic use, excessive fluid intake
Hyperuricemia in diuretic therapy
Hypoglycaemia due to phosphodiesterase-5-inhibitor

Impact of Co-Medications on Laboratory Result Interpretation of Diabetes Mellitus Patients:

Anti-hypertensive Medications:

The frequency of hypertension (HTN) among those with diabetes is almost twice that of non-diabetics.(7) This suggests either a common genetic or environmental factor in the pathogenesis or secondary complications of the diseases. Genetic variants in the gene encoding, adrenomedullin, angiotensinogen, apolipoprotein, and α-adducin have been reported to be associated with common conditions such as diabetes, hypertension, dysglycaemia, and/or metabolic syndrome [8]. In genome scans of a Chinese population, the region associated with diabetes was also associated with metabolic syndrome, which is a cluster of diseases including hypertension [9]. Moreover, prolonged hyperglycaemia leads to atherosclerosis which can cause the stiffening of arteries, increasing the peripheral resistance in the vessels and hypertension [10]. Hence, most diabetic patients are also on anti-hypertensive medications and antidiabetic medications concomitantly. Therefore, knowledge of the metabolic impact of anti-hypertensives will be helpful in the interpretation of biochemical profiles and management of diabetes mellitus [Table 2].

Table 2: Anti-Hypertensives-Induced Laboratory Changes in Diabetic Patients with Cardiovascular Complications

DRUGS	ASSOCIATED LABORATORY CHANGES
ACE Inhibitors	Azotaemia [11,12], Hyperbilirubinemia [41], elevates liver enzymes [41], reduces proteinuria [43]
Diuretics	
a. Thiazide	Dyslipidaemia [20-22], hypokalaemia [14], hyponatremia [14], hypomagnesemia [23], hypercalcemia[18],hyperglyceamia[24,25],hyperuricemia[27]
b. Loop	Hyponatremia[13],hypocalcemia[26],hypomagnesemia[23],hyperuricemia[27]
c. Potassium sparing	Hyperkalemia[27], metabolic acidosis[27]
Beta blockers	Dyslipidemia[28,29] ,hyperglycemia[34]
Centrally acting alpha 2 Adrenergic Agonist-methyldopa	Hyperbilirubinemia[37],elevates liver enzymes[37], hypernatremia[37], hyperchloremia[37] hypermagnesemia[37], hyperkalemia[37]

Angiotensin-converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs):

In the Action in Diabetes and Vascular Disease: Preterax(perindopril/indapamide) and Diamicron(gliclazide) Modified Release Controlled Evaluation (ADVANCE trial), sudden elevation in serum creatinine after starting perindopril-indapamide were associated with greater risks of subsequent major clinical outcomes. However, the continuation of angiotensin-converting enzyme inhibitor-based therapy reduced the long-term risk of major clinical outcomes, despite acute rise in creatinine[11].Increase in serum creatinine following the use of ACEI is largely attributed to a renin-angiotensin-aldosterone system (RAAS) inhibition-induced intraglomerular pressure decline (i.e.hypofiltration)[12].Discontinuation of ACEI is recommended if patients experience a ≥ 30% acute rise in serum creatinine after the commencement of treatment.Though, the long-term effects of its continuation or discontinuation on major clinical outcomes after such rise in serum creatinine is still unclear[11].

Diuretics:

Therapy with a loop or thiazide diuretics may lead to hypovolaemia, hyponatraemia, hypokalaemia, hypomagnesaemia, hyperuricaemia, hyperglycaemia, metabolic alkalosis and azotaemia[13].Thiazides also alters lipid profile causing an increase in serum total cholesterol, HDL-cholesterol, triglycerides, and bilirubin. Hypokalaemia is a sequela of the aldosterone-mediated actions of the Na/K pump in the collecting tubule of the nephron [14]. Thiazides doubtlessly have more potential to cause hyponatraemia than loop diuretics. Loop diuretics inhibit sodium (Na^+) transport in the renal medulla leading to prevention of the creation of a maximal osmotic gradient. Hence, loop diuretics impairs the renal concentrating ability [14]. On the other hand, the mechanism of action of thiazide diuretics is to decrease sodium reabsorption and therefore decrease fluid reabsorption. This directly causes decreased levels of circulating sodium. If hyponatraemia were to occur, it would happen during the first 2 to 3 weeks of therapy. After which, the patient is in a new steady state in which further sodium and water losses do not occur [14][15].Hypokalaemic metabolic alkalosis occurs due to the increase in aldosterone-mediated potassium and hydrogen ions excretion in the intercalated cells of the collecting tubules[16] [17]. Thiazide -induced hypercalcemia seems to result from increasing calcium reabsorption from the luminal membrane into the interstitium in exchange for sodium. Thiazides also reduce urine calcium levels

and increase blood calcium[18].Thiazide-induced hypokalaemia at the level of the pancreatic beta cells, causes hyperpolarization of the beta cell and decreases insulin secretion, leading to hyperglycaemia[19]. Thiazides act directly on the the organic anion transporter(OAT) 1 on the basolateral membrane of the proximal convoluted tubule to increase urate reabsorption and the OAT 4 on the luminal membrane of PCT where they are exchanged for urate.

The mechanism by which thiazides and thiazide-like diuretics induced hyperlipidaemia is largely unclear. However, thiazide diuretics appear to decrease catabolism while increasing synthesis [20]. Acute administration of high dose thiazide diuretics tend to increase sympathetic nervous activity and circulating noradrenaline that consequently promotes lipolysis, hepatic synthesis of cholesterol and apolipoproteins except Apoproteins A1 and A2 which are important component of HDL-C [20][21] [22]. Thiazide and loop diuretics increase urinary Mg^{2+} excretion which often coexists with hyponatraemia and hypokalaemia [23]. A combination of amiloride with hydrochlorothiazide, however, prevents glucose intolerance more than hydrochlorothiazide only[24][25].Loop diuretics induce natriuresis by inhibiting the Na-K-2Cl transporter in the thick ascending limb of the loop of Henle, causing increased urine calcium wasting and leading to hypocalcaemia with increased parathyroid hormone (PTH) level [26].On the other hand, hydrochlorothiazide and amiloride diminish calcium excretion by increasing calcium reabsorption from the luminal membrane into the interstitium in exchange for sodium at the NaCl transporter in the distal convoluted tubule leading to hypercalcaemia [26]. The potassium-sparing diuretics (amiloride, triamterene, mineralocorticoid receptor antagonists) can induce hyperkalaemia and metabolic acidosis and may also increase serum uric acid concentrations due to increased reabsorption in the proximal tubule [27]. Carbonic anhydrase inhibitors such as acetazolamide, ethoxazolamide, dorzolamide, brinzolamide can cause hypokalaemia and hyperchloremic metabolic acidosis by reversible inhibition of the carbonic anhydrase enzyme that causes decreased hydrogen ion secretion at the renal tubule and increases renal excretion of bicarbonate, potassium, sodium and water. Therefore, diabetes mellitus patients on diuretics should be closely monitored and their biochemical results should be interpreted on the background of their drug therapy.

Beta Blockers:
Monotherapy with beta adrenergic blockers such as atenolol and carvedilol for a period of one month to about three years could lead to increased LDL-C, urea, triglycerides, uric acid, potassium, glucose, and reduces HDL-C [28][29].Beta-blockers have been observed to reduce HDL-C and increase triglycerides. The inhibition of lipoprotein lipase has been implicated in several studies but the exact mechanism is not well understood, however, increase in alpha-adrenergic tone due to β-blockade result in the inhibition of lipoprotein lipase and decreased catabolism of triglycerides [30]. Consequently, circulating serum HDL decreases, while triglycerides increases. On the contrary, some β-blockers such as pindolol increase the activity of lecithin-cholesterol transferase leading to increase in HDL[31] [32]. Azotemia may set in when ACEIs or ARBs cause efferent arteriolar dilatation, thereby decreasing intraglomerular pressure and filtration[33]. Also, beta-blockers can potentially increase blood glucose concentrations and antagonize the action of oral hypoglycaemic drugs[34]. Therefore, a proper history of anti-hypertensive drug use is vital in the laboratory assessment of diabetes mellitus patients, especially at the pre-analytical testing phase. As such, drugs like thiazides and beta-blockers may be stopped three days before the laboratory test depending on the aim of the test.

Centrally-acting Alpha-2 Adrenergic Agonist:
Methyldopa causes a reduction in blood pressure via inhibition of adrenergic neuronal outflow leading to reduced total peripheral resistance and reduced blood pressure[35]. An attenuation of adrenergic neuronal outflow leads to a decrease in circulating norepinephrine levels which may lead to decreased insulin resistance. Thus, such drugs are thought to be beneficial in ameliorating glucose levels in pregnant women with gestational diabetes mellitus(GDM)[36]. However, it has been reported to increase ALP, bilirubin, urea, electrolytes (sodium, chloride, potassium and magnesium) as well as prolactin[37]. Moderate hyperprolactinemia caused by α- Methyldopa, is possibly caused by inhibition of the enzyme aromatic-l-amino-acid decarboxylase, which is responsible for converting L-dopa to dopamine, and by acting as a pseudo neurotransmitter to decrease dopamine synthesis. Though, Methyldopa is considered as the drug of choice in the treatment of non-complicated pregnancy-induced hypertension. However, methyldopa may cause hepatic necrosis through immunological reaction and there is some evidence to support the immunological mechanism. About 5% of nonpregnant women receiving methyldopa have been to have mild hepatitis [38]. Methyldopa may also cause increase in electrolytes by inducing dehydration. This may lead to hypovolemic-induced dyselectrolytemia.

ACE Inhibitors:
ACE inhibitors increase liver enzymes (AST, ALT, ALP), bilirubin, potassium, and Azotaemia (urea, creatinine), and reduce proteinuria. Though the ACE inhibitors are rare causes of clinically apparent liver injury[39]. They are considered first-line drugs for the treatment of hypertension and are considered particularly helpful in renoprotection of diabetes and hypertension[40]. ACE inhibitors have also been associated with acute liver injury that is usually cholestatic and self-limiting. The onset is typically within 1 to 8 weeks of starting the medication. Lisinopril is reported to be the most common cause of liver injury among the ACE inhibitors in clinical practice[41]. This may be misunderstood for a complication of metabolic syndrome such as non-alcoholic liver diseases. Thus, if this class of anti-hypertensive agents is indicated, close monitoring after commencement would be required.

Azotaemia emerges in ACE inhibitors or ARBs induced- efferent arteriolar dilatation, thereby reducing intraglomerular pressure and filtration[42]. Nevertheless, treatment with ACE inhibitors results in renal protection due to a reduction of systemic blood pressure, intraglomerular pressure, an antiproliferative effect, reduction of proteinuria and a lipid-lowering effect in proteinuric patients (secondary due to reduction of protein excretion)[43]. The rise in serum creatinine values usually begins a few days after initiation of ACE inhibitor or an ARB therapy, as it occurs due to reduction or blockade of angiotensin II levels. This results in efferent arteriolar dilatation and decreased effective GFR[44]. Therefore, a review of drug history may prevent a false assumption of new onset of renal insufficiency or worsening renal dysfunction in patients that had azotaemia at the commencement of ACEI regimen. Thus, discontinuation of ACEI may not be necessary unless serum creatinine level rise above 30% over baseline during the first 2 months after initiation of therapy or significant hyperkalemia of ≥5.6 mmol/L develops[45].

2. Anti-dyslipidemic Drugs:

Dyslipidemia is a very common finding in diabetes mellitus patient. It is estimated that 30-60% of patients with T2DM have dyslipidaemia[46]. Hyperglycaemia and postprandial hypertriglyceridemia, low HDL-cholesterol, elevated LDL-cholesterol and the predominance of small-dense LDL-cholesterol particles are typical characteristics of diabetic dyslipidaemia. These lipid profile changes underlie the pathologic link between diabetes mellitus and the increased risk of cardiovascular diseases[47]. To prevent cardiovascular complications most diabetes mellitus patients are placed on statins. Statins alter blood levels of glycated haemoglobin, glucose, AST, ALT, ALP, GGT, bilirubin, and creatinine phosphokinase. Some studies have suggested that statins may cause hyperglycaemia by increasing calcium concentration in the islet cells leading to a decrease in insulin release, or by decreasing GLUT 4-mediated peripheral glucose uptake[48]. Others have proposed that it increases insulin resistance and its secretion after 10 weeks of high-dose therapy[49]. Statin intake causes hyperglycemia. Glycated haemoglobin, a biomarker of long-term glycaemic control and fasting blood glucose are all influenced by statin intake. Although, statin therapy may decrease the risk of atherosclerotic cardiovascular disease but increases the risk of type 2 diabetes[49] [Table 3].

3. Antibiotics:

Hyperglycaemia with an associated immune compromise predisposes diabetics to infections and frequent use of antibiotics. Hyperglycaemia-induced neutrophil dysfunction which alters neutrophilic chemotaxis, phagocytosis and intracellular killing of the bacteria[50]. Also reduction in the quantity and function of lymphocytes in diabetics have been implicated as the major cause of immune compromise. Antimicrobials such as penicillins, aminoglycosides, macrolides, fluoroquinolones, amphotericin B and foscarnet may cause renal loss of potassium leading to hypokalaemia[51][52][53][Table 3].These antimicrobials are said to enhance delivery of sodium to the distal tubule where the reabsorption of sodium is done in exchange for potassium leading to wasting of potassium and hydrogen ions, eventually leading to hypokalaemia and concomitant metabolic alkalosis[54].

Electrolyte and acid–base imbalance have been attributed to aminoglycosides [55]. These are broad spectrum antibiotics commonly used for the treatment of aerobic gram-negative bacteria. They are often used in the treatment of severe infections of the abdomen and urinary tract, bacteraemia and endocarditis amongst others. Aminoglycosides have been linked with reversible tubular dysfunction without an associated change in glomerular filtration rate.and therefore, urine osmolality should be a preferred biochemical test in suspected aminoglycosides dysfunction than glomerular filtration rate determination because it is a potential cause of nephrogenic diabetes insipidus[52].

Normal therapeutic dosages of aminoglycosides have been reported to cause hypomagnesaemia in more than one-third of patients[56]. Hypomagnesaemia occurs early in therapy, as a result of renal magnesium wasting and may produce hypocalcaemia and hypokalaemia [57]. This Gitelman syndrome-like disorder has been associated with aminoglycoside use in many patients. Hypomagnesaemia is underscored by potentially severe symptoms such as neuromuscular and cardiac symptoms and it is also associated with symptoms and signs of metabolic abnormalities like hypocalcaemia, hypophosphatemia, and hypokalaemia[58]. Antibiotics–induced hypomagnesaemia can also occur during therapy with colistin and amphotericin B[51]. Antibiotics such as ciprofloxacin and trimethoprim-sulphamethoxazole interfere with creatinine result. While trimethoprim inhibits creatinine secretion and increases the serum creatinine concentration without affecting GFR, ciprofloxacin interferes with routine creatinine assay by reacting with picric acid giving a false positive result in vitro. Macrolides, metronidazole, penicillins, cephalosporins and tetracyclines(doxycycline) and fluoroquinolones (Ciprofloxacin) cause self-resolving transient increases in liver enzymes such as ALT, AST, LDH, Alkaline Phosphatase (ALP) and bilirubin, as well alters glucose results[59]. Hepatocellular injury or cholestasis can lead to elevation of serum enzyme ;. cases with short onset usually have more marked elevation of ALT levels, with occasional rapid worsening prolonged prothrombin time and early signs of hepatic failure. The mechanism of ciprofloxacin hepatotoxicity is suspected to be due to hypersensitivity which may present as hepatic complication of metabolic syndrome [60]. This mimics the hepatic complication of metabolic syndrome in T2DM. Moxifloxacin was found to be associated the most and ciprofloxacin the least with dysglycaemia. Therefore, caution should be taken in the interpretation of the results of patients on fluoroquinolones because this can be mistaken for poor glycaemic control due to other causes.

Macrolides have been implicated in azotaemia in elderly patients as a patient-associated risk factors.,However,the acute kidney injury caused by azithromycin is reversible[61]. In addition, ceftriaxones, azithromycin and nitrofurantoin but not clarithromycin may cause an increase in both urea and creatinine[62]. Cephalosporins are known potential nephrotoxins at high doses. Cefditoren, Tigecycline, Ertapenem, and Clarithromycin are associated with hypoglycaemia while azithromycin and Nitrofurantoin causes an elevation in serum glucose[63][64]. Amoxicillin alone or amoxicillin-clavulanic acid and cefelexin causes false positive or negative urine glucose[65]. Many antibiotics have been implicated in dysglycaemia when coadministered with hypoglycaemic agents, Hence may be considered during sample collection for glucose, as well as in the interpretation of results viz a viz clinical decisions of these patients[Table 2].

Table 3: Other Drug-Related Laboratory Changes in Diabetic Patients with Cardiovascular Complications

DRUGS	**ASSOCIATED LABORATORY CHANGES**
Fluoroquinolones Trimethoprim,penicillins,macrolides	Positive interference with creatinine assay[59,62]
aminoglycosides	Hypomagnesemia [56], hypocalcemia[57,58], hypophosphateamia[57,58], hypokalemia[57,58]
Penicillins, minoglycosides, macrolides, fluoroquinolones, amphotericin B, Forscanet	Hypokalemia[51-53], metabolic alkalosis[54]
Macrolides, nitroimidazole, penicillins, cephalosporins and tetracyclines and fluoroquinolones	Elevated liver enzymes (ALT,AST,LDH,ALP)[60]and bilirubin[60], dysglyceamia[59,63,64]
Macrolides, ceftriazones, azithromycin and nitrofurantoin	Azotemia[61,62]
Cefditoren,tigecycline,ertapenem and clarithromycin	Hypoglyceamia[63,64]
Azithromycin,Nitrofurantoin	Hyperglyceamia[63,64]
Amoxicillin,amoxicillin-clavulinic acid,cefelexin	False negative or positive glucosuria[65]
Statins	Hyperglycemia,elevated liver enzymes, hyperbilirubinemia, increased creatinine kinase[48,49]
Anti-inflammatory drugs	Hypervolemic hyponatremia[69-71]
Lactulose	Hypernatremia[84]
Cisplastin	Hypomagnesemia[90,91], hypokalemia[90-92]
Cyclosporine	Hyperkalemia[85],hypocalcemia[85] and hypomagnesemia[85]
Calcineurin inhibitors-Tacrolimus,Cyclosporine	Impaired glucose tolerance[85] and dysglyceamia[85]
Vitamin D	Increases creatinine[86], increases eGFR[86]
Sildenafil	Hypoglyceamia[94]

4. Anti-inflammatory drugs:

Overweight/obesity frequently co-exist with osteoarthritis (OA) in Type 2 diabetes mellitus (T2DM). Nearly half (47.3%) of patients with T2DM have some form of arthritis[66]. Although, excess body weight causes mechanical effect on joints which may be an underlying pathophysiological explanation of osteoarthritis of the lower limb. Diabetes mellitus has been reported to play a direct role in the pathophysiology of osteoarthritis via two major pathways involving oxidative stress and insulin resistance resulting to pro-inflammatory cytokines and advanced glycation end products (AGEs) production in joint tissues. This causes a low-grade chronic metabolic inflammation that can lead to structural joint damage. Insulin is a critical negative modulator of synovial inflammation and catabolism, therefore insulin resistance in obese individuals would diminish the suppressive capacity of insulin to production of inflammatory and catabolic mediators that promote OA[67].

Unfortunately, despite the well-recognised adverse effects of Non-Steroidal Anti-inflammatory Drugs (NSAIDs), the frequency of their utilization among diabetic patients with chronic complications such as hypertension, heart failure and chronic kidney disease (CKD), remains high[68]. NSAIDs inhibit cyclooxygenase (COX) (also known as prostaglandin H synthase). They also enhance the actions of Anti-diuretic Hormone (ADH) due to prostaglandin inhibition[69]. In clinical practice, water intoxication and hyponatraemia only occur with the use of NSAIDs in a state of endogenous or exogenous active ADH secretion, such as in elderly or neonatal patients, chronic renal failure, low salt diet, excessive oral water intake or heart failure, or concurrent analgesic use[70]. These scenarios are typical in diabetes mellitus patients with chronic complications. Therefore, knowledge of medication intake during result interpretation in this patient is vital to the prevention of post-analytical errors that may be misleading to clinicians. NSAIDs have been implicated as one of the commonest causes of hyponatraemia in elderly patients with T2DM[71] [Table 2].

5. **Gastrointestinal Drugs:**

Insulin resistance and hyperglycaemia are two major factors which play a significant role in gastrointestinal complications of diabetes mellitus. These complications include gastroesophageal reflux diseases (heartburn, acid reflux regurgitation and angina-pectoris-like pain), gastroparesis (early satiety, bloating, postprandial fullness, nausea, vomiting, or upper abdominal pain), intestinal enteropathy (diarrhoea, constipation, and faecal incontinence), and Non-Alcoholic Fatty Liver Disease (NAFLD). About a hundred million, meticulously organized neurons in the enteric nervous system controls the gut motility via the myenteric nerve plexus, and the absorption and secretion through the submucosal network [72]. The interstitial cells of Cajal (ICC) act as pacemaker, enabling the conveyance of impulses to the smooth muscles [72] Diabetes mellitus can chronically disrupt the GI tract's enteric, autonomic, and somatic nervous systems [72]. In hyperglycaemia, excess glucose molecules are diverted to alternative metabolic pathways like polyol, hexosamine, etc [73]. These glucose molecules attach avidly to fats or proteins leading to the formation of Advanced Glycation End products (AGEs) [73]. Free radicals and oxidative molecules leads to abnormalities in the structure and function of nervous system [74]. The reduced number of ICC, and accompanying damage to the smooth muscle and central nervous system (CNS) cells, may inadvertently cause contractile malfunction of the gut [75]. Furthermore, prolonged hyperglycaemia produces inflammatory changes and osmotic stress with resultant damage to vasa nervorum, contributing further to diabetic neuropathy [76]. Therefore, parasympathetic neural dysfunction due to diabetes resulting in alteration of digestive, secretory, absorptive and motor functions of the gastrointestinal tract leads to myriad of complications. Increased Helicobacter pylori (H. pylori) proliferation in gastrointestinal tract of T2DM is a major predisposing factor to peptic ulcer which may lead to catastrophic consequences such as bleeding and perforation [77]. Diabetes mellitus makes a patient prone to infection and gastroparesis diabeticorum. The duo may lead to microbial overgrowth in the upper gastrointestinal tract of diabetic patients with resultant increase incidence of peptic ulcer diseases and its complications in them. Hence, a strong association between the prevalence of H. pylori colonization and diabetes mellitus has been reported [77]. Therefore, many diabetes mellitus patients with chronic complications may be on some gastrointestinal drugs due to prevalent symptoms of GERD and these may influence laboratory results. Many diabetes mellitus patients are on H2 receptor inhibitors such as Cimetidine, Famotidine and Ranitidine. These drugs are known to decrease the secretion of creatinine by inhibiting it's secretion at the proximal tubule causing a decrease in renal clearance [78]. Cimetidine increase the serum creatinine concentration without affecting the true GFR. Moreover, dyselectrolytemia has been increasingly being associated with Proton pump inhibitors therapies such as hypokalaemia, hyponatraemia, hypomagnesaemia, hypophosphataemia and hypocalcaemia most especially in long-term therapy[79]. The very commonly used creatinine assay, the Jaffe method, is subject to interference by bilirubin and metabolic syndrome-associated pathophysiologic states, such as NAFLD which is often linked to hyperbilirubinemia, may create a negative interference. Bilirubin interferes with negatively the Jaffe method, leading to the under quantitation of creatinine concentrations. The resultant biliverdin generation in alkaline solutions due to oxidation of bilirubin diminishes the absorbance of both the creatinine picrate complex and bilirubin at the absorbance peak of 510 nm and increases the absorbance of biliverdin at the absorbance peak of 620 nm. In spite of better specificity of the enzymatic method, bilirubin can also interfere negatively with it, especially creatinine amidohydrolase based assay (creatininase). This interference may be attributable to the competition between bilirubin and the assay substrate for the H2O2 produced during the reaction. The falsely decreased creatinine results can have significant implications for the clinical management of patients. Moreover, the estimation of

the glomerular filtration rate and the measurements of creatinine clearance are highly dependent on accurate creatinine values which may adversely affect clinical decisions [80]. The most commonly reported gastrointestinal symptoms among diabetes mellitus patients is constipation [81]. The underlying aetiology of constipation in diabetes is multifactorial. In view of increased predisposition to autonomic and enteric neuropathy due to chronic hyperglycemia, there is an increased risk of altered colonic motility underlying constipation in diabetes mellitus patients than in the general population. It should also be noted that anorectal disorders are more common among these patients and can also contribute to constipation [82]. Smooth muscle structure and function, the density of the interstitial cells of Cajal, the health and function of the autonomic and enteric nerves of the colon are all potentially affected. Consequently, leading to alterations in colon motility and microbiome as well as immune and endothelial functions [83]. Lactulose is a bulk laxative used in the treatment of constipation. Hypernatremia has been reported infrequently in portal-systemic encephalopathy treatment with lactulose[84]. Due to its osmotic cathartic effects, the drug may cause faecal water loss in excess of sodium resulting in contraction of ECF volume and hypernatremia. This is usually a neglected cause of hypernatremia as most hypernatremia in diabetes mellitus patients is usually attributed to excessive use of diuretic antihypertensive[Table 2].

6. Immunomodulatory drugs:

Immunosuppressive drugs like calcineurin inhibitors are the cornerstone of immunosuppression for renal transplantation. Tacrolimus and cyclosporine are commonly used for renal transplantation which is more often done in diabetes due to the increased prevalence of diabetic nephropathy and end-stage renal disease. Cyclosporine is known to cause a combination of metabolic side effects including hyperkalaemia, hypercalciuria and hypomagnesaemia, as well as are increased creatinine, uric acid and urea. The calcineurin inhibitors are both known to reduce insulin release leading to decreased glucose tolerance and dyslipidaemia [85] [Table 2]. Vitamin D replacement therapy may be needed in chronic renal failure to prevent or treat renal osteodystrophy. However, it should be noted that vitamin D replacement modifies the production and release of creatinine increasing its blood levels, and reducing estimated glomerular filtration rates. The mechanism is said to be via a short-term vitamin D receptor activation increasing creatinine generation and serum creatinine, but it does not influence the glomerular filtration rate. Therefore, it may negatively affect the chronic renal failure classification which is based on the estimated glomerular filtration rate which in turn may lead to misjudgement of the clinical state of the patient [86] [Table 2].

Other prescribed Drugs

Anti-neoplastic drugs: Many epidemiological studies have associated diabetes mellitus with cancer. The risk of cancer has been said to increase with diabetes. Conversely, some cancers and their therapies have been implicated as a major cause of Diabetes Mellitus. Many studies have provided substantial evidence of associations between T2DM and risks of cancer in the mouth, lungs, gastrointestinal system, kidneys, bladder, thyroid, breast, ovaries, endometrium,white blood cells, glioma, and melanoma [87]. Gastrointestinal cancers such as cancer of the colon, pancreas and liver have been noted to have the highest risk of association with diabetes mellitus [88]. Therefore, some diabetic patients may be on anti-cancer therapy due to diabetes-associated cancer. Some anti-cancer drugs affect laboratory parameters such as electrolytes, creatinine, liver function test, etc. Chemotherapeutic drugs such as olaparib increase the secretion of creatinine in about 37% of individuals [89]. This may be mistaken for diabetic nephropathy if proper drug history is not taken. Cisplatin is commonly known to cause electrolyte imbalance. The electrolyte abnormality caused by cisplatin is mostly linked to hypomagnesaemia due to renal magnesium wasting. Others include hypernatremia, hypokalaemia, hypocalcaemia and hypophosphatemia. [90]. Cisplatin-induced hypomagnesaemia is mainly related to impaired magnesium reabsorption in the proximal tubule. However, cisplatin was depicted to down regulate the TRPM6/EGF pathway resulting in magnesium loss [91]. It causes an impairment of the calcium-sensing receptor leading to hypomagnesaemia. Subsequently, hypomagnesaemia causes an impaired release of parathyroid hormone which then leads to hypocalcaemia. Similarly, renal potassium loss occurs due to hypomagnesaemia resulting in hypokalaemia. Depletion of intracellular magnesium reverses the inactivation of voltage-dependent renal outer medulla potassium channels (ROMK), thus increasing kaliuresis. Kaliuresis is equally exacerbated by increased distal Na delivery or hyperaldosteronemia[92]. Potassium supplementation may fail to correct such hypokalaemia until hypomagnesaemia is corrected. Thus patients receiving platinum drugs can also develop persistent distal tubular dysfunction with a Gitelman-like syndrome characterized by hypocalciuria, hypomagnesaemia and hypokalaemic metabolic alkalosis. Cisplatin induces a syndrome of inappropriate secretion of ADH leading to hyponatraemia. It can decrease 1-α-hydroxylation activity resulting in reduced vitamin D3 levels, hypocalcaemia and a concomitant hypophosphatemia [93]. Drugs for Erectile dysfunction: Diabetics are prone to urinary tract infections (UTIs), cancer, bladder disorders and sexual dysfunction. Erectile dysfunction, is common in men who have diabetes, especially those with T2DM [94]. It is estimated that about 59.39% of men with diabetes have erectile dysfunction [94]. It may be a result of damage to nerves and blood vessels caused by poor long-term blood glucose control. Many diabetes mellitus patients are self-medicating or on sildenafil prescription, especially in developing countries where many myths are associated with impotence. Hypoglycemia has been observed following administration of sildenafil in some patients. This may also give an erroneous picture of good glycaemic control due to the transient effect of the drug. Therefore, a good drug history is very important in the interpretation of glucose results to ensure that the true state of the patient is reflected [Table 2].

Recommendations

Cardiovascular complications in diabetes mellitus patients predispose them to multiple drug use, and the drug history in this patient is paramount in the preparation of the patients for laboratory testing to ensure that an accurate, reliable and timely result is available for the management of patients. In order to achieve this the following should be done:

1. Provision and utilization of an effective Laboratory/ Hospital information system to ensure accessibility to the drug history of the patients.
2. Relevant clinical history including the patients' current drug history should accompany laboratory request forms in places where data collection and easy accessibility is still a challenge.
3. Referral systems should be established and enforced to keep track of patients' information as they move from one health facility to another.
4. Provision of affordable health insurance to improve funding of health care facilities to enable them to provide alternative drugs whenever it becomes necessary in the management of these patients.

Conclusion

Good knowledge of the drug history of diabetic patients will ensure that an accurate, reliable and timely result which is fit for purpose is produced from the laboratory for improved management outcomes

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