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Elite Journal of Medicine. Volume 2 issue 3(2024), Pp. 14-27
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Influence of Glycaemic Control and Microvascular Complications on Oxidative Stress in Patients with Type 2 Diabetes Mellitus: A Cross-sectional Study in Kano, Nigeria

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Abstract

Increase in oxidative stress accelerates the risk of cardiovascular events in diabetes mellitus (DM) by inducing inflammatory reactions and endothelial dysfunction This research was aimed to determine the effect of glycaemic control and microvascular complications on oxidative stress biomarkers (SOD, GPx, CAT and MDA) in patients with type 2 DM in Kano, Nigeria. Study comprised of 300 participants divided into four (4) groups: 1 Non diabetics as Controls; 2 patients with DM diagnose less than five years without complications; 3 patients with DM diagnose greater than five years without complications and 4 diabetic patients with complications. Group 4 was sub-categorised into diabetic Nephropathy, Retinopathy, Neuropathy and multiple microvascular complications. Mean FBG (mmol/L) concentration in controls group was lower ($p< 0.05$) than DM<5 years without complications, DM>5 years without complications and DM with complications however, Retinopathy, Nephropathy, Neuropathy, multiple Complications, and those of diabetic without complications, shows no significant difference ($p>0.05$). FBG in patients with Good Glycaemic Control were lower than those with Inadequate Glycaemic Control and Poor Glycaemic Control (<0.05). Those with Poor Glycaemic Control, however, showed higher FBG

Citation: Bunza JM, Alhassan AJ, Sani MU, Gwarzo MY, Ogunwale KA, Haruna S, Ciroma FA, Dallatu MK, Jidda ML, Ngaski AA, Kwaifa IK, Kasimu M, Yale BM, Aliyu KB, Obeagu EI. Influence of Glycaemic Control and Microvascular Complications on Oxidative Stress in Patients with Type 2 Diabetes Mellitus: A Cross-sectional Study in Kano, Nigeria. Elite Journal of Medicine, 2024; 2(3): 14-27

concentration than patients with Inadequate Glycaemic Control (<0.05). Plasma SOD, GPx and CAT activities in the controls group was significantly higher, while MDA was lower, than in the DM<5 years without complications, DM>5 years without complications and DM with complications, however, The mean the Diabetic Retinopathy, Nephropathy, Neuropathy and Multiple complications showed no significant difference (*p*>0.05). Plasma SOD, GPx and CAT activities in patients with Good Glycaemic Control was significantly higher while MDA was lower, than those in Inadequate Control and Poor Control groups (<0.05). DM and glycaemic poor glycaemic control caused lower antioxidants enzymes activities in the patients but showed insignificant difference between patients with microvascular complications and those without.
Keywords: *DM, glycaemic control, microvascular complications, SOD, GPx, CAT, MDA*

Introduction

Diabetes mellitus (DM) is a serious, long-term condition that occurs when raised blood glucose levels persist because the body cannot produce any or adequate insulin or cannot effectively use the insulin it produces (1). Insulin is an essential hormone produced in the pancreas. It allows glucose from the bloodstream to enter the cells of the body where it is converted into energy or stored. Insulin is also essential for the metabolism of protein and fat. A lack of insulin, or the inability of cells to respond to it, leads to high levels of blood glucose (hyperglycaemia), which is the clinical indicator of DM (1). It is estimated that, the number of people with DM Worldwide as at 2021 was about 537million (1). In Africa alone about 24 million people are diabetic (1). In Nigeria about 3.6 million have diabetes mellitus (1). Incidence of DM is expected to rise, with the projection of 783 million worldwide and 55 million in Africa by 2045 (1).

The endogenous antioxidants comprise of the enzymatic antioxidants such as Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), Glutathione Reductase (GR), Catalase (CAT), and non-enzymatic antioxidants including glutathione (GSH), α-lipoic acid, vitamins C and E (2). On the other hand, the exogenous antioxidants include micronutrients and other exogenously administered compounds such as vitamin E, vitamin C, trace metals (selenium, manganese, zinc), carotenoids and flavonoids (3).

An increase in oxidative stress accelerates the progression of atherosclerosis and increases the risk of cardiovascular events by inducing inflammatory reactions, endothelial dysfunction, thrombogenic tendency, plaque instability, and the migration, proliferation, and transformation of smooth muscle cells. In patients with DM, oxidative stress is elevated due to glucose auto-oxidation, enhanced glycation, activated AGEs-RAGE axis, enhanced polyol pathway, impaired glutathione redox cycle, and activated PKCs, among others (4). The production of ROS in mitochondria is also increased in patients with DM. Even in normal physiological situations, superoxides are generated as byproducts of oxidative phosphorylation in the mitochondrial electron transport chain, but when blood glucose levels are high, glycolysis is enhanced, which consequently increases the flow of electrons to the mitochondrial electron transport chain and the production of superoxides in cells (5).

Lipid peroxidation is the free radical oxidation of polyunsaturated fatty acids (PUFAs) such as linoleic acid or arachidonic acid, and it is capable of extensive tissue damage. ROS-induced peroxidation of membrane lipids, in fact, alters the structure and the fluidity of biological

membranes, which ultimately affect their function. Among the most frequently studied markers of lipid peroxidation are isoprostanes such as 8-iso-prostaglandin F2α (8-iso-PGF2α), MDA, thiobarbituric acid reactive substances, and hydroxynonenal (HNE) (Bigagli and Lodovici, 2019). MDA is a highly reactive nucleophilic agent generated by both lipid peroxidation and as a by-product of prostaglandin and thromboxane synthesis that can attack macromolecules, including amino acid or sulfhydryl moiety of proteins leading to alterations in their functions. HNE as a major toxic aldehyde generated by ROS attack to ω-6 polyunsaturated fatty acids and reacts with proteins forming advanced lipoxidation end products. Both HNE and MDA adducts were detected in atherosclerotic lesions (6). Bioactive products of lipid peroxidation induce disturbances in membrane organization, functional loss, and modifications of enzymes, carriers, and cytoskeletal and mitochondrial proteins as well as DNA bases leading to cell death or inducing alterations in the biochemical properties of these biomolecules (7)
This research work was aimed to determine the effect of glycaemic control and microvascular complications on oxidative stress biomarkers (SOD, GPx, CAT and MDA) in patients with type 2 DM in Kano, Nigeria.

Materials and Methods

Study Area/ Population

The study was conducted at the Department of Medical laboratory Sciences, Faculty of Allied Health Sciences, College of Health Sciences, Bayero University, Kano. The study participants were drawn from the hospital around Kano metropolis (Murtala Specialist Hospital, General Hospital Nasarawa and Aminu Kano Teaching Hospital, Kano).
The total number of 300 study participants was recruited from males and females with type 2 DM attending diabetic clinics at Murtala Specialist Hospital, General Hospital Nasarawa and Aminu Kano Teaching Hospital, Kano and age matched apparently healthy individuals used as controls were recruited around the metropolis. The participants were divided into four groups: DM duration less than five years without complications, DM duration more than five years without complications, DM with Microvascular complications and apparently healthy controls.

Ethical Consideration

Ethical approval for this research was obtained from the Ethics and research Committee of Hospital Services Management Board, Kano State Ministry of Health, Kano. Ethical consideration was in line with Helsinki declaration. A written informed consent was obtained from all the study participants prior to inclusion in the study.

Assessment for Microvascular Complications

The patients were examined for the presence of any of the diabetic complications using clinical examinations and Laboratory investigations. Diabetic Nephropathy was diagnosed using Urinary Albumin Creatinine Ratio (ACR). Retinopathy was established by an ophthalmologist and the

patients were already receiving care in ophthalmology unit. Neuropathy was established using clinical examination by the presence of symptoms such as pains and use of monofilament examination with the help of physician. The prevalence of the complications determined after all the samples were collected.

Sample Collection

Four (4) ml of whole blood each was collected from the median cubital vein, using vacuutainer blood collection kits, into the EDTA and Lithium Heparin container. The lithium heparin anticoagulated blood was centrifuged at 3000 rpm for five minutes to separate the plasma. The separated plasma was transferred in to cryovials and stored at -20^{o} C until used for the analysis of biochemical parameters. The EDTA anticoagulated blood was used for HbA1c analysis.

Spot urine was collected into the universal bottle for the determination of urinary Albumin Creatinine Ratio (ACR).

Laboratory Analysis

Super Oxide Dismutase, Glutathione Peroxidase and Catalase activities were analysed using ELISA, Malondialdehyde was analysed by colorimetric method, Glucose was estimated using Gucometer (Glucose oxidase-peroxidase), HBA1c using Ion exchange chromatography, albumin using microalbuminuria minikit, Creatinine using Jaffe's method.

Data Analysis

The continuous data generated from Plasma glucose, HBA1c, SOD, GPx and CAT from the laboratory analysis was analyzed using IBM SPSS statistical software version 25 (Armonk, New York: IBM Corp). One-way ANOVA was used to analyse and compare the numerical outcomes which followed normal distribution. Significant difference for any outcome was further analyzed by Bonferoni's Post hoc tests. The significant level was set to be 0.05 at 95 % confidence interval.

Results

The current study comprised of four (4) groups. Group one (1) were Non diabetic apparently healthy participants as Controls; group two (2) were patients with diabetes mellitus diagnose less than five (5) years without complications; group three (3) were patients with diabetes mellitus diagnose greater than five (5) years without complications and group four (4) were diabetic patients with complications. Group four (4) was sub-categorised into diabetic Nephropathy, Retinopathy, Neuropathy and multiple microvascular complications. The results were presented as mean ± standard error (SE) of the mean of the outcome. Bonferoni's Post hoc test was further used to analyse the mean outcome of the significant difference across the group with p value set at <0.05 at 95 % confidence interval.

The mean FBG (mmol/L) concentration in the controls group (4.56 ± 0.07), as illustrated in Table 1, was significant lower (p< 0.05) compare to the levels in DM<5 years without complications (11.61 ± 0.65), DM>5 years without complications (10.97 ± 0.57) and DM with complications (11.90 ± 0.56), however, the levels in the respective groups with DM show no significant difference (p>0.05). The mean FBG comparisons, as illustrated in Table 2, between patients with Retinopathy (12.75 ± 0.67), Nephropathy (12.61 ±0.98), Neuropathy (11.34 ± 1.02), multiple

Complications (11.08 ±0.86) and those of diabetic without complications (11.29 ± 1.39), shows no significant difference (p>0.05), however, they are significantly higher than that of controls (p<0.05).

The mean comparisons of plasma SOD activity were illustrated in Table 1 across the groups. The SOD activity in the controls group (1.93 ± 0.05) was significantly higher than in the DM<5 years without complications (1.74 ± 0.04), DM>5 years without complications (1.76 ± 0.05) and DM with complications (1.74 ± 0.22) (p<0.05). The mean SOD activities, as illustrated in Table 2, in the Diabetic Retinopathy (1.73 ± 0.05), Nephropathy (1.66 ± 0.03), Neuropathy (1.83 ± 0.04) and Multiple complications (1.75 ± 0.04) subgroups showed no significant difference (p>0.05).

The mean comparisons of plasma GPx activity were illustrated in Table 1 across the groups. The GPx activity in the controls group (75.42 ± 2.28) was significantly higher than in the DM<5 years without complications (57.25 ± 1.79), DM>5 years without complications (58.94 ± 1.70) and DM with complications (56.91 ± 1.66) (p<0.05). The mean GPx activities, as illustrated in Table 2, in the Diabetic Retinopathy (54.89 ± 1.46), Nephropathy (58.61 ± 1.65), Neuropathy (51.82 ± 1.45) and Multiple complications (63.32 ± 1.30) subgroups showed no significant difference (p>0.05).

The mean comparisons of plasma CAT activity were illustrated in Table 1 across the groups. The Cat activity in the controls group (130.88 ± 2.36) was significantly higher than in the DM<5 years without complications (111.90 ± 1.96), DM>5 years without complications (107.99 ± 2.22) and DM with complications (106.68 ± 1.92) (p<0.05). The mean CAT activities, as illustrated in Table 2, in the Diabetic Retinopathy (110.30 ± 1.84), Nephropathy (104.63 ± 1.81), Neuropathy (106.15 ± 1.72) and Multiple complications (107.02 ± 1.63) subgroups showed no significant difference (p>0.05).

The mean comparisons of plasma MDA concentrations were illustrated in Table 1 across the groups. The MDA concentration in the controls group (0.89 ± 0.03) was significantly lower than in the DM<5 years without complications (1.55 ± 0.05), DM>5 years without complications (1.57 ± 0.04) and DM with complications (1.61 ± 0.05) (p<0.05). The mean MDA activities, as illustrated in Table 2, in the Diabetic Retinopathy (1.59 ± 0.05), Nephropathy (1.58 ± 0.05), Neuropathy (1.58 ± 0.05) and Multiple complications (1.69 ± 0.05) subgroups showed no significant difference (p>0.05).

The mean comparisons of FBG concentration (mmol/L), SOD, GPx, CAT activities and MDA concentration across the various levels of glycaemic controls were illustrated in table 3. The mean FBG concentration (mmol/L) in patients with Good Glycaemic Control (5.95 ± 0.12) were significantly lower than those with Inadequate Glycaemic Control (8.87 ± 0.15) and Poor Glycaemic Control (15.47 ± 0.37) (<0.05). Those with Poor Glycaemic Control, however, showed higher FBG concentration than patients with Inadequate Glycaemic Control (<0.05). The mean SOD activity in patients with Good Glycaemic Control (1.85 ± 0.03) was significantly higher than

those in Inadequate Control (1.66 ± 0.14) and Poor Control (1.73 ±0.03) (<0.05). The mean GPx activity in patients with Good Glycaemic Control (64.21 ± 1.50) was significantly higher than those in Inadequate Glycaemic Control (54.98 ± 3.41) and Poor Glycaemic Control (58.67 ± 1.38) (<0.05). The mean CAT activity in patients with Good Glycaemic Control (118.58 ± 1.67) was significantly higher than those in Inadequate Control (106.01 ± 4.29) and Poor Glycaemic Control (108 ± 1.67) (<0.05). The mean MDA concentration in patients with Good Glycaemic Control (1.24 ± 0.04) was significantly lower than those in Inadequate Glycaemic Control (1.74 ± 0.12) and Poor Glycaemic Control (1.63 ± 0.04) (<0.05).

Table 1: The mean comparisons of FBG, plasma SOD, GPx, CAT and MDA activities in patients with type 2 DM with and without complications and controls

Groups	**FBG (mmol/L)**	**SOD (IU/L)**	**GPx (IU/L)**	**CAT (IU/L)**	**MDA (µmol/L)**
Controls	4.56 ± 0.07[a]	1.93 ± 0.05[a]	75.42 ± 2.28[a]	130.88 ± 2.36[a]	0.89 ± 0.03[a]
DM<5years No Complication	11.61 ± 0.65[b]	1.74 ± 0.04[b]	57.25 ± 1.79[b]	111.90 ± 1.96[b]	1.55 ± 0.05[b]
DM>5years No Complication	10.97 ± 0.57[b]	1.76 ± 0.05[b]	58.94 ± 1.70[b]	106.68 ± 1.92[b]	1.57 ± 0.04[b]
DM with Complication	11.90 ± 0.56[b]	1.74 ± 0.22[b]	56.91 ± 1.66[b]	106.68 ± 1.92[b]	1.61 ± 0.05[b]
F value	44.627	4.254	24.824	27.957	54.789
P value	<0.05	<0.05	<0.05	<0.05	<0.05

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One way ANOVA data presented as mean ± standard error of the mean. *P* value of < 0.05 was considered significant. Values with different superscript have significant difference.

Table 2:Mean comparisons of FBG, plasma SOD, GPx, CAT and MDA activities in patients with type 2 DM with various microvascular complications and controls

Groups	FBG (mmol/L)	SOD (IU/L)	GPx (IU/L)	CAT (IU/L)	MDA (µmol/ml)
Controls	4.56 ± 0.07[a]	1.93 ± 0.05[a]	75.42 ± 2.28[a]	130.88 ± 2.36[a]	0.89 ± 0.03[a]
DM without Complication(s)	11.29 ± 1.39[b]	1.75 ± 0.03[b]	58.09 ± 1.23[b]	109.95 ± 1.48[b]	1.57 ± 0.3[b]
Retinopathy	12.75 ± 0.67[b]	1.73 ± 0.05[b]	54.89 ± 1.46[b]	110.30 ± 1.84[b]	1.59 ± 0.05[b]
Nephropathy	12.61 ±0.98[b]	1.66 ± 0.03[b]	58.61 ± 1.65[b]	104.63 ± 1.81[b]	1.58 ± 0.05[b]
Neuropathy	11.34 ± 1.02[b]	1.83 ± 0.04[ab]	51.82 ± 1.45[b]	106.15 ± 1.72[b]	1.58 ± 0.05[b]
Multiple Complications	11.08 ±0.86[b]	1.75 ± 0.04[b]	63.32 ± 1.30[b]	107.02 ± 1.63[b]	1.69 ± 0.05[b]
F value	27.133	2.950	15.152	16.531	33.077
P value	<0.05	<0.05	<0.05	<0.05	<0.05

One way ANOVA data presented as mean ± standard error of the mean. *P* value of < 0.05 was considered significant. Values with different superscript have significant difference.

Table 3: Mean comparisons of FBG, plasma SOD, GPx, CAT and MDA activities in patients with type 2 DM with various levels of glycaemic control

Glycaemic Control	FBG (mnol/L)	SOD (IU/L)	GPx (IU/L)	CAT (IU/L)	MDA (µmol/ml)

Good	5.95 ± 0.12[a]	1.85 ± 0.03[a]	64.21 ± 1.50[a]	118.58 ± 1.67[a]	1.24 ± 0.04[a]
Inadequate	8.87 ± 0.15[b]	1.66 ± 0.14[b]	54.98 ± 3.41[b]	106.01 ± 4.29[b]	1.74 ± 0.12[b]
Poor	15.47 ± 0.37[c]	1.73 ±0.03[b]	58.67 ± 1.38[b]	108 ± 1.67[b]	1.63 ± 0.04[b]
F value	368.837	4.087	4.592	9.384	30.284
P value	<0.05	<0.05	<0.05	<0.05	<0.05

Glycaemic Control (Good = HBA1c <7%, Inadequate = HBA1c 7-8%, Poor = HBA1c >8%). One way ANOVA data presented as mean ± standard error of the mean. *P* value of < 0.05 was considered significant. Values with different superscript have significant difference.

Discussion

In the current study, the plasma antioxidant enzymes activities were assessed across the groups. The plasma SOD, GPx and CAT activities were analysed as measure of antioxidant activity in the study population. The SOD, GPx and CAT activity in the controls group was significantly higher than in the DM<5 years without complications, DM>5 years without complications and DM with complications ($p<0.05$). The mean SOD, GPx and CAT activities in the Diabetic Retinopathy, Nephropathy, Neuropathy, Multiple complications subgroups and DM without complications showed no significant difference ($p>0.05$). The current research focus was on enzymatic antioxidants which SOD, GPx, and CAT. The current study is in agreement with the work of Najafi et al. on Oxidant/antioxidant status in Type 2 DM patients, at the Isfahan University of Medical Sciences, Isfahan, Iran, which showed that the Plasma activities of SOD, GPx and CAT in patients with type 2 DM was significantly higher than that of non-diabetic controls and that the patients with microvascular complications had lower activities that those without complications. The current study is consistent with the work of Sheweita et al. on the changes in oxidative stress and antioxidant enzyme activities in streptozotocin-induced DM in rats, who reported that the activities of SOD, GPx, and CAT were significantly decreased in the streptozotocin-induced diabetic rats compared to those of the control group. Sheweita *et al*. however, did not study these activities in microvascular complications of DM. the reason for such derangement in antioxidant enzymes is explained by Ayepola *et al.* that, free radicals produced under physiological conditions are maintained at steady state levels by endogenous or exogenous antioxidants. Oxidative stress occurs when the production of free radicals overwhelms the capacity of cellular antioxidant system, as in DM, causing biological damage. Due to their ability to directly oxidize and damage DNA, proteins, and lipids, free radicals are believed to play a key role in the onset and progression of late-diabetic complications. Other mechanisms of increased generation of ROS is by reducing the activities of enzymatic antioxidant such as SOD and CAT, lowering of glutathione stores, and activation of PKC as seen in DM. Cecilia *et al*. reported that when the production of ROS is higher than the antioxidant defenses, oxidative stress occurs and at that point, cellular and mitochondrial function

get affected. Oxidative stress has been considered one of the most important factors in the development of Diabetic Retinopathy in chronic hyperglycemia and also plays a role in the formation of ROS due to the activation of the secondary pathways such as the polyol and PKC (10). The current research, however, is not in agreement with the report of Ma *et al*. which showed that the performance of these antioxidants are damaged in DM and that the degree of damage is more pronounced in patients with diabetic complications; whereas, the current study found no significant difference between diabetic patients with or without microvascular complications. Also contrary to this study, Kumawat *et al*. reported in a paper titled "Antioxidant Enzymes and Lipid Peroxidation in Type 2 Diabetes Mellitus Patients with and without Nephropathy" carried out at Swami Man Singh Medical College, Jaipur, Rajasthan, India, which showed that the intensity of oxidative stress predicted by SOD, GPx and CAT in Type 2 diabetic patients with nephropathy is greater when compared with Type 2 diabetic patients without nephropathy as compared to the controls; whereas, the current study showed no difference except for controls.

In the current study, the plasma MDA concentrations were assessed across the groups. The MDA concentration in the controls group was significantly lower than in the DM<5 years without complications, DM>5 years without complications and DM with complications (p<0.05). The mean MDA activities in the Diabetic Retinopathy, Nephropathy, Neuropathy and Multiple complications subgroups showed no significant difference (p>0.05). To support the current findings, Gwarzo & Muhammad reported in a paper titled "evaluation of hypoglycaemic effect and antioxidant property of *Entada abyssinica* leaves powder on alloxan induced diabetic mice" that MDA is increased in diabetic rats compared to non-diabetic controls. Similarly, Ahmad et al. in a paper titled "Antioxidative and anti hyperglycaemic effect of *Calotropis procera* in alloxan induced diabetic rats" published that, concentration of the MDA across the diabetic groups were significantly higher in non-diabetic controls. This study is also in agreement with a previous study (3), which reported a reduction in the MDA level, in both fasting and postprandial states of type 2 diabetic patients compared to controls. Ma *et al*. also reported that oxidative stress, as evident from the altered levels of antioxidant enzymes and oxidative stress markers, is characterised by higher levels of MDA in Type 2 DM. Also in concordance with the current study, a research carried out at Swami Man Singh Medical College, Jaipur, Rajasthan, India by Kumawat et al. (2013) observed that there were higher MDA values in Diabetic Nephropathy and DM without the complication than the corresponding controls; indicating no much difference between the group with nephropathy and that without the Nephropathy. Also in a paper titled "Oxidant/antioxidant status in Type2 DM patients" conducted at the Isfahan University of Medical Sciences, Isfahan, Iran, Najafi et al. showed that the Plasma MDA in patients with type 2 DM was significantly higher than that of non-diabetic controls. The current study is also consistent with the work of Sheweita et al. on the changes in oxidative stress and antioxidant enzyme activities in streptozotocin-induced DM in rats who reported that the concentration of MDA was significantly higher in the streptozotocin-induced diabetic rats compared to that of the non-diabetic control group. It is believed that the hyperglycemia associated with hyperlipidaemia could be the causative factor for the increased production of free radicals and lipid peroxides (MDA). In patients with

DM, there is an increased production of free radicals which promotes lipid peroxidation. The intermolecular cross linking of collagen through MDA leads to its stabilization and allows further glycation. This in turn increases the potential of glycated collagen to initiate further lipid peroxidation. Also, defective pentose phosphate pathway as seen in type 2 DM led to the peroxidation of polyunsaturated fatty acids in the cell membrane (11, 13-33).

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Citation: Bunza JM, Alhassan AJ, Sani MU, Gwarzo MY, Ogunwale KA, Haruna S, Ciroma FA, Dallatu MK, Jidda ML, Ngaski AA, Kwaifa IK, Kasimu M, Yale BM, Aliyu KB, Obeagu EI. Influence of Glycaemic Control and Microvascular Complications on Oxidative Stress in Patients with Type 2 Diabetes Mellitus: A Cross-sectional Study in Kano, Nigeria. Elite Journal of Medicine, 2024; 2(3): 14-27

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