Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/14619
DOI URL: http://dx.doi.org/10.21474/IJAR01/14619

RESEARCH ARTICLE

DIABETES MELLITUS- IN A POST COVID ERA, ITS ORAL ASPECT AND DIAGNOSIS: A REVIEW

Dr. Rohit Mishra, Dr. K.T Chandrashekar, Dr. Tanvee Mahawar and Dr. Deeksha Sharma

Manuscript Info

Manuscript History
Received: 28 February 2022
Final Accepted: 30 March 2022
Published: April 2022

Key words:-
Diabetes Mellitus, Periodontitis, COVID 19, Point of Care Testing, POCT

Abstract

Diabetes mellitus is a group of physiological impairment characterized by hyperglycaemia resulting from defect in insulin secretion, insulin action or both.This disease can lead to many complications in various regions of the body, the oral complications that can be seen are xerostomia, dental caries, gingivitis, periodontal disease, increased tendency to oral infections etc. Periodontal disease is the only 6th complication of diabetes mellitus.[1,2] In summer 2021, the covid-19 second wave in India has raised more consequential concerns about the ability of this infection to trigger the glucogenic machinery in Covid patients, possibly leading to the new onset of diabetes mellitus. The purpose of this review is to summarizes the chairside diagnosis of Diabetes mellitus and its oral aspects by a periodontist specially in post Covid era.

Introduction:-

Diabetes mellitus is a group of physiological impairment characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both.[1]The diabetic cases can be classified as either Type I or Type II , gestational diabetes mellitus and diabetes due to other causes such as neonatal diabetes and maturity-onset diabetes of the young, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes.This disease can lead to many complications in various regions of the body, the oral complications that can be seen are xerostomia, dental caries, gingivitis, periodontal disease, increased tendency to oral infections etc.[2]

Hyperglycemia is estimated to be the third highest risk factor for premature mortality by World Health Organisation.[3-6]Type II diabetes mellitus was found to be the most prevelant cause for diabetes accounting for almost all cases of undiagnosed patient. Worldwide 463 million of the total population are affected by diabetes mellitus among them around 232 million were unaware of their diseased condition.[4,7,8.]

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) or the 2019 novel coronavirus (2019-nCoV) as it was known previously,has spread across the world from its origin in Wuhan city of Hubei Province of China.[9]

The symptoms of Covid – 19 include fever, headache, dry cough, sore throat, dyspnea, abdominal discomfort, vomiting and diarrhea.The oral manifestations include ulcers, swelling, erythema, halitosis, plaque, spontaneous bleeding etc.[10]

Corresponding Author:- Dr. Rohit Mishra

Methodof Review:-

A comprehensive electronic search was conducted on PUBMED/MEDLINE, GOOGLE SCHOLAR, and HAND SEARCH of reference list of archieved articles. The research search strategy used the key words and medical subject headings terms and a combination for the effective search result.The search terms used were "Diabetes mellitus" OR "Covid -19"OR "Periodontitis" OR "Periodontal disease" OR "Oral Health" OR "POINT OF CARE TESTING" OR "Point of care devices" OR "REVIEW" OR "RCT" OR "Randomized controlled trials" OR "Clinical Trials". Out of these searches a total number 38 articles were selected .A combination of all these terms are used for the exhaustive research paper.

Diabetes,Covid -19 &Periodontitis: A new relationship

Dental professional, since long have been recognising the association between the two highly prevalent conditions i.e diabetes and periodontitis. It has been established through various epidemiological studies that diabetes is a risk factor for periodontits. The risk is three times more as compared to non diabetic patients especially when glycemic control in poor.[11]In a Pima Indian study in Arizona, loss of periodontal attachment and bone loss wasgreater in diabetic patients compared to non-diabetic patients of various age groups.[12,13]

Accumulation of subgingival biofilm initiates the inflammation in the periodontal tissue.[14]The tissue damage consequencing from the chronic inflammation in the periodontal tissues (loss of attachment, breakdown of periodontal ligament fibres and alveolar bone resorption) is majorly irreversible.[15]

Patient with type 1 or type 2 diabetes or periodontal disease reflects an imbalance or hyper-release of soluble cytokines in response against the synergistic factors.[16]Tobacco use, stress and the action of viruses are the other risk factors for periodontal disease and diabetes respectively.In response to the presence of these modifiers**,** cells from both diabetics and periodontal patients release increased levels of certain cytoactive chemicals**.** Prostaglandin E2(PGE2), interleukin 1 (IL1) and tumor necrosis factor α (TNFα) being the example. In 1998 W.A soskolne demonstratedthe relationship between periodontal disease and diabetes.[17]

In an invitro study the upregulation of the immune response mediators by comparing diseased animals with healthy controls to explain the relationship between periodontal disease and diabetes.

The prevalence of periodontitis is increased in diabetes along with the extent and severity of the disease. Patient with diabetes sometimes presents with case of multiple recurring periodontal abscess.

Other oral condition associated with diabetes are gingival overgrowth, lichenoid mucosal reaction from metformin,xerostomia,risk for caries, candida infection,recurring mouth ulcers.The association of diabetes and periodontitis involves aspects of inflammation, immune functioning, neutrophil activity, and cytokine biology.[18]Accumulation of reactive oxygen species, oxidative stress, and interactions between advanced glycation end products (AGEs) in the periodontal tissues and their receptor (RAGE, the receptor for advanced glycation end products) all add to increased inflammation in the periodontal tissues in people with diabetes.[18]

Diabetes and Covid-19: A New Relationship?

The presentation of Severe acute respiratory syndrome corona virus -2 (SARS- CoV-2) infection present as ranges from asymptomatic infections with spontaneous recovery, to severe illness. Severe and critical illness of Covid19 is presented and, associated with acute viral pneumonia which requires oxygen support and often with assisted mechanical ventilation[18]

In India the second wave of Covid 19 hadcrucialconcerns about the ability of this infection to trigger the glucogenicmachinery in Covid patients, leading to new onset diabetes mellitus.[19,20]

New onset diabetes mellitus has two proposed factors they are damage to beta cells in the pancreas and its impaired function and/or development of insulin resistance (IR).[21]Pancreatic beta cells have high levels of Angiotensin converting enzyme 2(ACE2) receptors Viral entry into the islet cells containing betacells of pancreas is facilitatedthrough these receptors.[22]These viruses are supposed to cause damage to the islet cells in pancreas, and cause downregulation of ACE2 receptors leading to increased angiotensin levels, and impair the insulin secretion.[23]

This entity of "new-onset" hyperglycemia could be classified as:

1. Stress-induced hyperglycemia
2. New-onset diabetes in previously unrecognized pre-diabetes
3. Hyperglycemia possibly related to SARSCoV-2 direct effect on pancreas and
4. Drug-induced hyperglycemia or "secondary diabetes" during the course of treatment for COVID-19, especially with frequent use of corticosteroids.[20]

Nishindra Kinjalk et al in Aug 2021- Observational prospective of series of studies;of adult Covid 19 cases in hospitals in north India, during the early summer 2021, discovered that they had no prediabetes and no prediction of diabetes. On admission, they had high blood sugar and needed insulin. After they were discharged from hospital they needed insulin or Oral Antidiabetic medications. Eight weeks after follow up, these cases continued to require antidiabetic medicines.Diagnosis of new onset diabetes must be kept in mind with every case of SARS CoV-2 infection, even after full recovery from acute Covid -19.[24]

Brynn E. Marks et al in September 2021 in a retrospective comparative study concluded that the cases of Type II Diabetes mellitus increased by 182% with a six times increase in Diabetic ketoacidosis.[25]

Catherine E. Barrett et al in January 7 2022 conducted a study in which patients with <18 years of age with COVID-19 are more likely receive a new diabetes diagnosis >30 days after infection than were those without COVID-19 and those with pre pandemic acute respiratory infections.[26]

What is point of care Testing (POCT)?
Papyrus was the first to document POCT in 1500BC. Ants were used by Egyptian physicist to detect glycosuria in patients with undiagnosed diabetes.

Extralaboratory or near-patient testing are the other terms used for POCT and is defined as testing that is performed near or at the site of a patient with the result leading to a possible change in the care of the patient.[28]

This procedure can be performed by taking adrop of capillary whole blood via finger prick for the testing of HbA1C in most of the point of care testing devices. Following the application to the test cartridge, the sample is then analyzed based on the methods analysing the difference between the charge or structure of glycated and non-glycated haemoglobin.[28]

Mechanism Of POCT:
POCT technologies can be split under two categories. These technologies have been definitely refined and improved to deliver easier-to-use devices with incremental improvements in analytical performance.

The first is small handheld devices, providing qualitative or quantitative determination of an increasing range of analytes.The second category of devices are larger, often bench-top devices which are essentially laboratory instruments which have been reduced in both size and complexity.[27]

Cation-exchange chromatography:
Hemoglobin species (HbA1c and HbA0) are separated based on the difference in isoelectric point, by employing differences in ionic interactions between the hemoglobin in the blood sample and the cation interchange groups on the column resin surface. Separation is gained by employing differences in ionic interactions between the cation exchange group on the column resin surface and the hemoglobin constituent in the provided sample. A hemolysis reagent is used to dilute the whole blood sample to release haemoglobin by breaking up the red blood cells for analysis.An autosampler is used to inject the hemosylate into the analytical column of a known volume.A programmed buffer gradient of increasing ionic strength (the mobile phase) is delivered to the column and the hemoglobins are then separated based on their ionic communication with the column material.[27,30]

Immunoassay:
The immunoassay method uses antibodies that bind to the N-terminal glycate tetrapeptide or hexapeptide group of HbA1c, forming immunecomplexes**.**which can be detected and measured by means of a turbidimeter or a nephelometer.[27]

The excess antibodies agglutinate after binding to HbA1c, a turbidimeter or nephelometer is used to measure the resultant turbidity from the immunocomplexes.[27,30]

Affinity chromatography:
Affinity chromatography is a separation technique based on structural differences between glycated vs non-glycated hemoglobin which utilizes m-aminophenylboronic acid and its specific interactions with the glucose adduct of glycated hemoglobin .

A whole-blood sample hemolysate is applied to the affinity column and the glycated hemoglobinwhich contains cis-diols coplanar groups strongly interacts with immobilised boronic acid on an agarose gel. Ionic and hydrophobic forces also addon to this interaction.[27,30]

Enzymatic assay:
Enzymatic quantification of HbA1c is based on cleavage of the beta chain of haemoglobin by specific proteases to liberate peptides, which then further react to produce a measurable signal.[28]

The whole blood sample after lysis are prone to substantial proteolytic digestion; this process involves amino acids being released, including glycated valines, from the hemoglobin β-chains. In the direct enzymatic HbA1c assay, glycated valines serve as substrates for a specific recombinant fructosyl valine oxidase enzyme.[28,30]

Point of care testing devices (POCT)
The requirement of point of care device is increasing immensely over few years with the advantage of prompt availability of results.

There are various POCT devices available and the performance of these devices are variable.[30]
POCT devices currently available for HbA1c analysis are:

A1cNow+ (PTS/Chek diagnostics
The A1cNow+ analyser is presently the smallest portable device, which requires capillary or venous blood. The principle for analysis of HbA1c is based onimmunoassay.

Concerning accuracy, six studies, with a minimum of 47 and a maximum of 1618 patient samples, reported a wide overall bias range of -12.0 to +21.9 mmol/mol (-1.1% to +2%)[29]

Aurélie Affretet al in December 2015 concluded that the A1CNOW+ has good sensitivity.[31]

A1c Gear (Sakae Corporation
The A1c Gear HbA1c analyser uses an immunoassay method (immuno-turbidimetric) and only requires a small sample of capillary or venous blood to deliver results within six minutes.[30]

Adetoun ejilemele in may 2014 conducted a study in which it was concluded that the a1cgear is a precise device.[32]

SD A1c Care (SD Biosensor)
The lightweight POCT device manufactured by SD Biosensor has a short analysis time of three minutes using an immunoassay-based procedure. [30]

DCA 2000(+) and DCA Vantage (Siemens Medical Diagnostics)
It is a discontinued and has been modified by the manufacturers to the DCA vantage has a better interface but uses the same reagents and basic methodology as the previous model.There are till a large number of DCA 2000(+) analysers in use and therefore information on the instrument is still relevant.

Yeo CP et al., in a study used 80 samples from people with diabetes, the DCA 2000 showed a total CV of 3.4% at a low HbA_{1c}, and at a higher level a CV of 7.3%.[33]

Ean Szymezak et al in 2008 conducted a study in which it was concluded thatDCA Vantage analytical and practical characteristics very suitable for HbA_{1c} assay for laboratory or point-of-care use according to good laboratory practice.[34]

InnovaStar (DiaSys)
Using the turbidimetric immunoassay approach, the InnovaStar HbA1c equipment analyses HbA1c levels in 6.5 minutes. The test procedure requires users with laboratory experience and as such may limit its role as a point of care device.[35]

Afinion: (F.D.A Approved)
The Afinion AS100 Analyzer is comfortable to learn and use. TheDCA2000+ and Afinion AS100 Analyzer have similar footprints on the bench and are comparable in environmental requirements like operating temperature, humidity, power, and need for a level bench that is stable during operation.The DCA2000+ and Afinion AS100 Analyzer are not designed to be portable. Because both analyzers weigh 11 pounds, they are better suited to a physician's office or satellite laboratory with dedicated space rather than being brought to the patient's bedside. However, this is where the similarities end. The Afinion AS100 Analyzer is faster (3 minutes to result versus 6 minutes for the DCA2000+), stores more data (up to 500 patient and 500 control results), and is barcode compatible for scanning specimen and reagent labels. Staff had very positive comments regarding the ease of use, particularly sample loading during analysis.[36]

Other point of care testing devices commercially available are ERA-STAT 2000**,**Clover**,**HemoCue Hba1c 501 System,HumaMeter A1c**,** Labona- Check A1c, Nycocard**,**Quo-Lab HbA1c Analyser**,**Quo-Test**,**Tri-Stat HGB A1C.

Hyung-Doo Park in February 2021 in a review article concluded that POCT can help clinicians make expeditious medical decisions and with improvement of point of care testing technology the area use is also expanding [37]

Future Considerations
In future the point of care device is likely to play a increasing role in the health care delivery simultaneously increasing the efficacy of service provided to the patient [38]

Conclusion:-

The increasing incidence of new onset diabetes associated with Covid -19, cautions the healthcare providers, as well as the population at risk, to be vigilant about the glycaemic control in post Covid period.Screening is more cost-efficient than treating the disease and could reduce the economic burden of diabetes care.As healthcare providers, it is the responsibility dental professionals to raise awareness of diabetes. Future research on the assessment of diabetes in the dental setting need to be carried out to better understand the value of screening in the dental setting, and to explore if this form of screening leads to improved diagnosis and management of diabetes.More research is needed to augment on the expanded scope for Point of care screening for T2DM in the dental setting to demonstrate utility and effectiveness particularly in the low- and middle-income countries with high incidence of undiagnosed T2DM is high.

Reference:-

1. American Diabetes Association, “Diagnosis and classification of diabetes mellitus,” Diabetes Care, vol. 33, supplement 1, pp. S62–S69, 2010.
2. American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes care. 2017 Jan 1;40(Supplement 1):S11-24.
3. World Health Organization, Global Health Risks—Mortality and Burden of Disease Attributable to Selected Major Risks, WHO, Geneva, Switzerland, 2009.
4. E. M. Hadlaq, Z. T. Faraj, F. M. Al Gamdi, F. A. Al Obathani, M. F. Abuabat, and K. H. Awan, “Early screening of diabetes and hypertension in primary care dental clinics at King Saud University in Riyadh, Kingdom of Saudi Arabia,” e Journal of Contemporary Dental Practice, vol. 18, no. 8, pp. 652–659, 2017.
5. L. J. Giblin, L. Rainchuso, and A. Rothman, “Utilizing a diabetes risk test and A1c point-of-care instrument to identify increased risk for diabetes in an educational dental hygiene setting,” Journal of Dental Hygiene: JDH, vol. 90, no. 3, pp. 197–202, 2016.

6. N.-C. R. Holm, D. Belstrøm, J. A. Østergaard, S. Schou, P. Holmstrup, and M. B. Grauballe, "Identification of individuals with undiagnosed diabetes and pre-diabetes in a Danish cohort attending dental treatment," Journal of Periodontology, vol. 87, no. 4, pp. 395–402, 2016.
7. International Diabetes Federation, IDF Diabetes Atlas, Vol. 9, International Diabetes Federation, Brussels, Belgium, 2019.
8. G. M. Stein and A. A. Nebbia, "A chairside method of diabetic screening with gingival blood," Oral Surgery, Oral Medicine, Oral Pathology, vol. 27, no. 5, pp. 607–612, 1969.
9. Wang Chen, Horby Peter W, Hayden Frederick G, Gao George F. A novel coronavirus outbreak of global health concern. *The Lancet*. 2020;395(10223):470–473.
10. Iranmanesh B, Khalili M, Amiri R, Zartab H, Aflatoonian M. Oral manifestations of COVID-19 disease: A review article. Dermatologic therapy. 2021 Jan;34(1):e14578.
11. Mealey B L, Ocampo G L. Diabetes mellitus and periodontal disease. Periodontol 2000 2007; 44: 127–153.
12. Lalla E, Lamster IB, Schmidt AM. Enhanced interaction of advanced glycation end products with their cellular receptor RAGE: implications for the pathogenesis of accelerated periodontal disease in diabetes. Ann Periodontol. 1998;3:13-9. 16.
13. Shlossman M, Knowler WC, Pettitt DJ, Genco RJ. Type 2 diabetes mellitus and periodontal disease. J Am Dent Assoc. 1990;121:532-6.
14. Preshaw P M, Alba A L, Herrera D et al. Periodontitis and diabetes: a two-way relationship. Diabetologia 2012; 55: 21–31
15. Jowett A K, Orr M T, Rawlinson A, Robinson P G. Psychosocial impact of periodontal disease and its treatment with 24h root surface debridement. J Clin Periodontol 2009; 36: 413–418
16. Iacopino AM, Cutler CW. Pathophysiological relationships between periodontitis and systemic disease: recent concepts involving serum lipids. J Periodontol. 2000;71:1375-84
17. Soskolne WA. Epidemiological and clinical aspects of periodontal diseases in diabetics. Ann Periodontol. 1998;3:3-12
18. Taylor J J, Preshaw P M, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. J Clin Periodontol 2013; 40 (Suppl 14): S113–134.
19. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020; 323:1061–1069.
20. Singh AK, Singh R. Hyperglycaemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract. 2020;1 67:108382.
21. Muniyappa R, Gubbi S. COVID-19 pandemic, corona viruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5): E736–41
22. Rubino F, Amiel SA, Zimmet P, et al. New-onset diabetes in Covid-19. N Engl J Med. 2020; 383:789–790
23. Steenblock C, Richter S, Berger I, Barovic M, Schmid J, Schubert U, Jarzebska N, von Mässenhausen A, Linkermann A, Schürmann A, Pablik J. Viral infiltration of pancreatic islets in patients with COVID-19. Nature communications. 2021 Jun 10;12(1):1-2.
24. Kinjalk N, Kinjalk T, Prasad KN, Kinjalk A, Kinjalk M. New Onset Diabetes Mellitus In Second Wave Of Covid -19 Patients In North India. International Journal Of Scientific Research. 2021 August
25. Marks BE, Khilnani A, Meyers A, Flokas ME, Gai J, Monaghan M, Streisand R, Estrada E. Increase in the Diagnosis and Severity of Presentation of Pediatric Type 1 and Type 2 Diabetes During the COVID-19 Pandemic. Hormone research in paediatrics. 2021;94(7-8):275-84.
26. Barrett CE, Koyama AK, Alvarez P, Chow W, Lundeen EA, Perrine CG, Pavkov ME, Rolka DB, Wiltz JL, Bull-Otterson L, Gray S. Risk for Newly Diagnosed Diabetes> 30 Days After SARS-CoV-2 Infection Among Persons Aged< 18 Years—United States, March 1, 2020–June 28, 2021. Morbidity and Mortality Weekly Report. 2022 Jan 14;71(2):59.
27. Sharma S, Zapatero-Rodríguez J, Estrela P, O'Kennedy R. Point-of-care diagnostics in low resource settings: present status and future role of microfluidics. Biosensors. 2015 Sep;5(3):577-601.
28. ISO22870:2006. Point-of-care testing (POCT) —requirements for quality and competence Geneva: International Organization for Standardization; 2006
29. Affret A, Griz LH, Cesse EA, Specht YD, Carvalho EM, Fontbonne A. Assessment of a glycated hemoglobin point-of-care analyzer (A1CNow+) in comparison with an immunoturbidimetric method: a diagnostic accuracy study. Sao Paulo Med J. 2015.

30. English E, Milosovich ET, John WG. In vitro determination of hemoglobin A1c for diabetes diagnosis and management: technology update. Pathology and Laboratory Medicine International. 2014;6:21-31
31. Affret A, Griz LH, Cesse EÂ, Specht YD, Carvalho EM, Fontbonne A. Assessment of a glycated hemoglobin point-of-care analyzer (A1CNow+) in comparison with an immunoturbidimetric method: a diagnostic accuracy study. Sao Paulo Medical Journal. 2015 Apr 14;133:460-4
32. Ejilemele A, Unabia J, Ju H, Petersen JR. A1c Gear: laboratory quality HbA1c measurement at the point of care. Clinica chimica acta. 2015 May 20;445:139-42.
33. Yeo CP, Tan CH, Jacob E. Haemoglobin A1c: evaluation of a new HbA1c point-of-care analyser Bio-Rad in2it in comparison with the DCA 2000 and central laboratory analysers. Annals of Clinical Biochemistry. 2009;46:373-6.
34. Szymezak J, Leroy N, Lavalard E, Gillery P. Evaluation of the DCA Vantage analyzer for HbA1c assay. Clinical chemistry and laboratory medicine. 2008 Aug 1;46(8):1195-8.
35. Jensen EA. A system for measurement of HbA1c manufactured by DiaSys Diagnostic Systems GmbH. SKUP (Scandinavian evaluation of laboratory equipment for primary health care), 2014.
36. Arabadjief M, Nichols JH. Evaluation of the Afinion AS100 point-of-care analyzer for hemoglobin A1C. Point of care. 2009 Mar 1;8(1):11-5.
37. Park HD. Current status of clinical application of point-of-care testing. Archives of Pathology & Laboratory Medicine. 2021 Feb 1;145(2):168-75
38. Chem. 2010;56(1):44–52. 49. Lenters-Westra E, English E. Evaluation of four HbA1c point-of-care devices using international quality targets: are they fit for the purpose? J Diabetes Sci Technol. 2018;12(4):762–770.