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RESEARCH ARTICLE

CHARACTERISTICS OF DIABETES MELLITUS DEVELOPED POST-COVID-19 INFECTION IN ADULTS

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Abstract

Background: This integrative review aimed to identify the specific criteria researchers have used in their studies to classify and treat post-COVID-19 Diabetes Mellitus (DM) compared to other types of DM recognized by the International Diabetes Federation (IDF) and the World Health Organization(WHO).

Materials and Methods: In this study, an integrative review of the literature was used. The search strategy began with three electronic databases (CINAHL, Coronavirus Research, and MEDLINE/PubMed). Considering the inclusion criteria, published studies that examined the new onset or early onset of DM post-COVID-19 infection in adults were chosen. Data extraction and analysis were completed on all included studies. The final sample for this integrative review comprised 20 studies.

Results: The findings of this integrative review indicated the demographic and physiological variables associated with post-COVID-19 DM compared to the other types of DM (T1DM, LADA, and T2DM). These findings have been divided into three themes: Theme 1—the nomenclature of post-COVID-19 DM; Theme 2—the individual risk factors for developing post-COVID-19 DM including the subthemes of demographic variables and physiological variables (lab tests); and Theme 3- Post-COVID-19 DM treatment.

Conclusion: In general, the findings of this integrative review highlighted that post-COVID-19 DM might be considered a novel form of DM with unique genetic features. This integrative review called attention to the need for further research on post-COVID-19 DM.

Introduction:-

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. In 2021, approximately 536.3 million adults aged 20–79 years globally were living with a type of DM [1]. Globally, DM is one of the largest clinical and public health challenges on public health and socioeconomic development [1]. Thus, diabetes is considered as one of the top 10 causes of mortality globally [2]. Uncontrolled DM is associated with several metabolic complications and failure of organs [1]. The global cost of diabetes and its consequences are expected to reach US$2.1 trillion by 2030 [3].

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Another huge global burden on public health and socioeconomics is the COVID-19 pandemic and it has been estimated to have a global total cost of more than US$16 trillion [4]. Globally, COVID-19 is characterized by high infection rates of more than 676 million positive cases and by high mortality rates with more than 6 million deaths [5].

There is a potential pathological link between COVID-19 and DM [6]. COVID-19 is associated with multiorgan failure [7] and leads to profound alterations in whole-body metabolism [6]. Sustained inflammation affects systemic glucose homeostasis and contributes to hyperglycemia [6], insulin resistance [7], and β-cell destruction, which influences diabetes pathology [6].

Although the alternation in glucose metabolism is one of the DM complications, COVID-19 has been associated with alternation in glucose metabolism as well [8,9]. Specifically, ketoacidosis was observed during and after COVID-19 infection [8]. The alternation in glucose metabolism and ketoacidosis might be considered an indirect clinical indicator of a lack of insulin, possibly due to β-cell loss or malfunction [8]. Thus, COVID-19 is associated with β-cell destruction leading to DM [8].

Interestingly, researchers have indicated that those who have not been previously diagnosed with DM have developed DM post-COVID-19 infection [10]. Although the association between COVID-19 and the risk of developing DM post-COVID-19 infection is still unclear; it has been suggested that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may lead to downregulation of the insulin signaling pathway resulting in insulin resistance [10]. SARS-CoV-2 may infect and replicate in islet β-cells of the pancreas, altering insulin secretion [11]. Thus, it may be considered a distinctive type of DM having the ability to alter insulin efficiency and availability [10,11], which requires a specific therapeutic plan to be managed effectively [10].

Distinguishing post-COVID-19 DM from other types of DM is important for proper diagnosis and a treatment plan. The International Diabetes Federation (IDF) and the World Health Organization (WHO) have established criteria to classify DM types based on demographic and physiological factors, such as age and specific lab tests [1,12]. Accurate diagnosis of DM classification is critical for effective treatment as each type of DM has a therapeutic protocol [13]. Upon initial diagnosis, patients with type 1 diabetes mellitus (T1DM) require immediate insulin as their pancreas doesn't produce insulin, while latent autoimmune diabetes of adults (LADA) patients can initially produce insulin, delaying replacement for 6-12 months [13].

Conversely, type 2 diabetes mellitus (T2DM) patients can initially manage with lifestyle changes and pharmacological therapy, allowing effective use of the insulin produced by their pancreas (see Table 1) [13].

Table 1:-Variables to differentiate between different types of DM [13,14].

Variable	T1DM	LADA	T2DM
Risk factors for developing DM			
Demographic variables			
Age	<25	≥ 18	>25
Family history of diabetes	5–10%	>75–90%	Hist of T1DM OR T2DM
No history of diabetes	Yes	Yes	Yes
Physiological variables			
Genetics and immunity markers			
Autoantibodies (ICA & Anti-GAD)	Positive	Positive	Negative
Interleukin-6 (IL6)	High	High	Increases the level
HLA DR1-DR3-DQ2 genes	Positive	Positive	Negative
Diabetes-specific lab tests			
History of normal HbA1c	No	Varies	Varies
High blood glucose level	Yes	Yes	Yes
C-Peptide	Low to undetectable	Normal then low	Normal then low

Ketoacidosis risk	High	Low	Low
Insulin treatment			
Time to require insulin	At onset	Within 6 months	Can be many years
Insulin dependency	Yes	Within 6 months to 1 year	Varies

Currently, there are no official guidelines exist for classifying or treating COVID-induced diabetes [10]. There's a pressing need for increased comprehension in preventing complications associated with undiagnosed or inadequately managed DM [1].

Methodology:-

This study followed an integrative literature review design according to Whittemore and Knafl [15]. This design has been used to specify the review purpose and provide a more systematic rigorous approach to understanding, classifying, and treating post-COVID-19 DM compared to other types of DM recognized by the IDF and the WHO [14].

Step 1: problem identification

Although post-COVID-19 DM is still considered a novel form of DM, there is an increasing number of researchers investigating this phenomenon. Despite numerous studies on post-COVID-19 DM in adults, the novelty of post-COVID-19 DM requires an examination of existing literature. This analysis aims to identify the specific criteria used by researchers to classify and treat post-COVID-19 DM in relation to demographic and physiological variables compared to other types of DM recognized by the IDF and the WHO. Given the current impact of COVID-19 on the different body organs, the integrative literature review is mandatory to help healthcare practitioners and researchers to better understand post-COVID-19 DM in adults.

Step 2: literature search

Using a search strategy designed with the assistance of a professional librarian, a search was conducted to examine existing literature on the new or early onset of DM in adults with post-COVID-19 infection worldwide. The literature search has been conducted using the keywords shown in Table 2. Boolean connectors, such as “and” and “or” were used to search the literature.

Table 2:-

Population terms	**Adults**
Diabetes terms	(Diabetes) AND ((New onset) OR (Early onset))
Covid terms	(Covid19) OR (Coronavirus) OR (COVID-19) OR (Cov-19) OR (sars-cov-2) OR (2019-ncov)

Search terms

The following three databases were searched: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Coronavirus Research, and Public/Publisher MEDLINE (PubMed) databases. These databases were chosen because of their potential to answer the review question as they publish health sciences and COVID–19–related articles. Additional articles were identified through snowballing.

Inclusion/exclusion criteria

Inclusion criteria

Each article was assessed for inclusion according to the following eligibility criteria. The eligibility criteria for being included were for each article: (a) to be full text, (b) to be published in English, and (c) only the articles of adult participants. The participants above 18 years of age are considered because the legal age for adulthood in the state of Qatar is 18 years [16]. The articles included adults who developed a new onset of DM post-COVID-19 infection. The participants of the included articles had no history of DM or were prediabetic before being infected by COVID-19.

Exclusion criteria

Articles of pediatric populations with individuals aged less than 18 years old had been excluded. Non-peer-reviewed articles have been excluded to avoid the inclusion of any poor-quality research. Articles of new-onset DM post-COVID-19 vaccination, new-onset hyperglycemia, or new-onset insulin resistance DM post-COVID-19 infection have been excluded because these articles did not have the potential to reach the objectives of the study.

Screening

All articles (393 articles) were exported to Covidence software for screening. A PRISMA flow diagram was then used to further screen the studies for relevance and potential inclusion in the present review [17]. To ensure rigor, this integrative review was conducted under the supervision of an experienced researcher. The studies screening has been conducted by two different researchers, the disagreement between them regarding the inclusion and exclusion criteria has been resolved by discussion. A total of 393 articles were imported from three different databases and snowballed (see Figure 1).

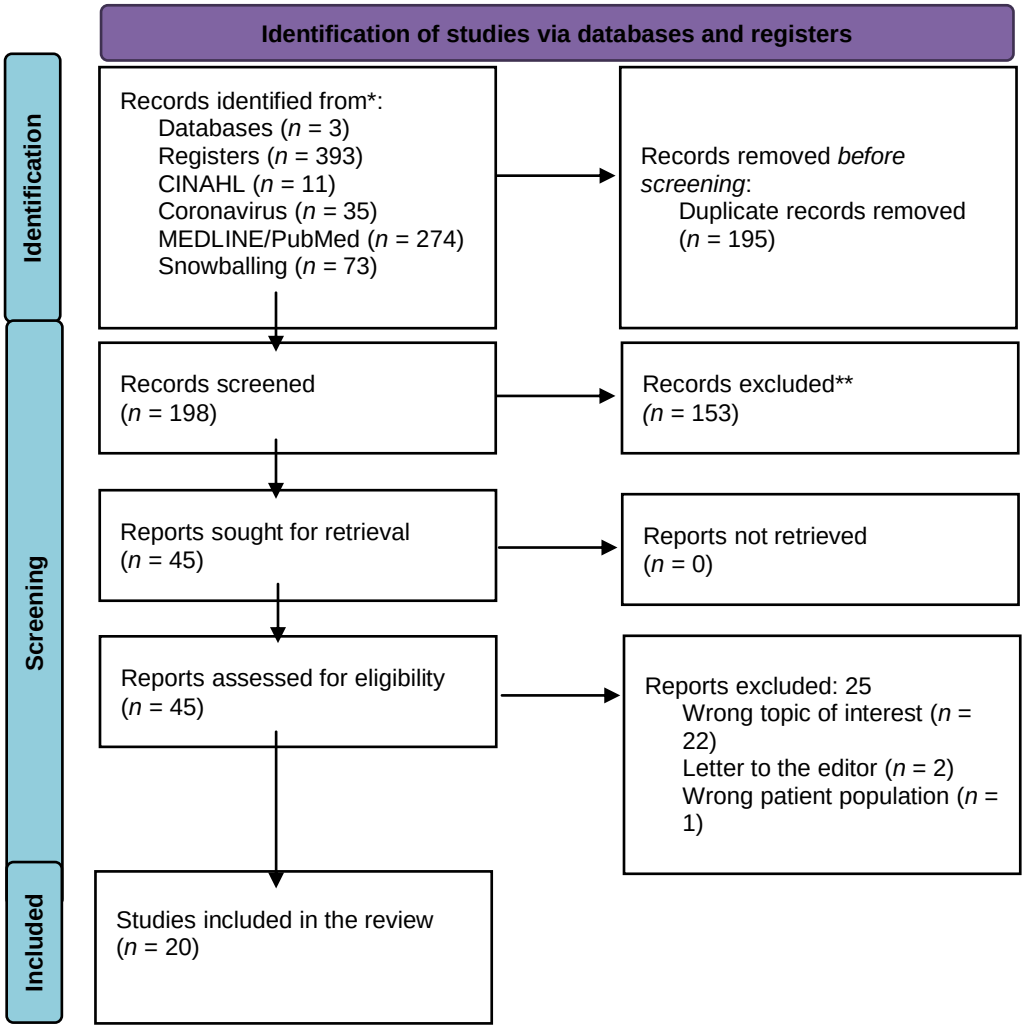

Figure 1:- PRISMA flow diagram.

Characteristics of included studies

The selected studies had a wide range of different study designs, including four case reports, four case series, one case-control study, one cross-sectional study, one prospective observational cohort study, six retrospective cohort studies, one literature review study, two systematic reviews, and meta-analysis studies. Studies included the population of different countries—the United States and India have six studies each describing their population, two studies describing China's population, and one study each covering Ethiopia, France, Poland, Germany, Spain, and

the United Kingdom respectively. The sample size ranged from one to three patients in case reports and case series; up to hundreds in cohort studies. All studies included were conducted between March 2020 and December 2022.

Step 3: data evaluation

The Joanna Briggs Institute (JBI) [18] critical appraisal tools were used to evaluate the 20 included studies and assess the overall quality. JBI's critical appraisal checklists have been used because it has a specific checklist for each type of research design [18]. Out of the 20 studies, 15 had been evaluated as high-quality studies that met all the criteria of JBI [18] and five as medium quality due to the lack of follow-up. The quality assessment has been conducted by two different researchers with no disagreement on the evaluation. The inclusion of only high- and medium-quality studies enhances the credibility of the recommendations of this integrative review.

Step 4: data analysis

While Whittemore &Knafl [15] acknowledge undeveloped methods for integrative review analysis, they recommend the six steps of thematic analysis developed by Braun and Clarke [19].As a first step, through repeated readings, researchers gained familiarity with the data and captured initial ideas. Then, the demographic and physiological criteria were used as a framework to look for the criteria used currently by researchers prior to coding, to conduct suitable codes, such as hyperglycemia, ketoacidosis, and DM treatment. The relevant data in each of the included articleswas collected under the appropriate code. After that, the data were reduced into categories by highlighting and extracting the findings from each primary source. Then, the data extracted from various primary sources were displayed in networks and matrices to facilitate the comparison across all primary sources. After that, all data were compared to identify the different themes to be grouped in; thus, similar variables were grouped next to each other and under one theme. All data have been grouped into three main themes: the nomenclature of post-COVID-19 DM, post-COVID-19 DM treatment, and the individual risk factors for developing post-COVID-19 DM. Finally, the conclusion was provided by integrating the analyzed data.

Step 5: data presentation

Data presentation is the outline of the integrative review results. The discussion and implication of the integrative review results are considered a part of the data presentation.

Results:-

This integrative literature review identifies the specific criteria that researchers have used in their studies to classify and treat post-COVID-19 DM which has been divided into three themes: Theme 1—the nomenclature of post-COVID-19 DM; Theme 2—the individual risk factors for developing post-COVID-19 DM including the subthemes of demographic variables, and physiological variables (lab tests); and Theme 3—post-COVID-19 DM treatment.

The findings of this integrative review indicated the demographic and physiological variables associated with post-COVID-19 DM in comparison to the other types of DM (T1DM, LADA, and T2DM). Different factors from the 20 included studies were integrated into five categories. Afterward, based on the common meanings and the relationships between the categories, commonalities collapsed into three main themes. The themes included: the nomenclature of post-COVID-19 DM, the individual risk factors for developing post-COVID-19 DM, and post-COVID-19 DM treatment. Variables within each theme were found to influence post-COVID-19 DM positively or negatively. Table 3 summarizes the findings in the literature of the criteria that researchers have used to differentiate post-COVID-19 DM compared to other established types of DM.

Table 3:-Variables to differentiate between different types of DM and post-COVID-19 DM.

Variables	T1DM	LADA	T2DM	Post-COVID-19 DM
Risk factors for developing DM				
Demographic variables				
Age	<25	≥18	>25	No specific age
Family history of diabetes	5–10%	>75–90%	Hist of T1DM or T2DM	Unclear
No history of diabetes	Yes	Yes	Yes	Yes
Physiological variables				
Genetics and immunity markers				

Autoantibodies (ICA and anti-GAD)	Positive	Positive	Negative	Negative
Interleukin-6 (IL6)	High	High	Increases the level	Varies
HLA DR1-DR3-DQ2 genes	Positive	Positive	Negative	Positive
Diabetes-specific lab tests				
History of normal HbA1c	No	Varies	Varies	Varies
High blood glucose level	Yes	Yes	Yes	Yes
C-Peptide	Low to Undetectable	Normal then Low	Normal then Low	Normal
Ketoacidosis risk	High	Low	Low	Varies
Insulin treatment				
Time to require insulin	At onset	Within 6 months	Can be many years	At onset
Insulin dependency	Yes	Within 6 months to 1 year	Varies	At onset then diminishes

Theme 1: the nomenclature of post-COVID-19 DM

The first theme presents the nomenclature of post-COVID-19 DM. It is important to know how researchers have classified those who have developed DM post-COVID-19 infection because this has implications for their treatment plan. Some researchers have used the diagnosis of T2DM and the T2DM treatment protocol despite knowing the fact that the variables/lab tests were not aligned with T2DM [20].

Theme 2: individual risk factors for developing post-COVID-19 DM

The second theme describes the variables that make a person a risk factor for developing post-COVID-19 DM, either demographic or physiological variables. It is important to know the risk factors associated with post-COVID-19 DM development to differentiate between post-COVID-19 DM and the other typesaccording to the IDF and WHO classification, which has been used as a framework to assess the criteria because this has implications on assigning the proper DM therapeutic plan and prevention protocol [1,11].

Demographic variables

The first subtheme presents demographic variables which include age, gender, and past medical status, and risk variables include body mass index (BMI), family history of DM, comorbidities, pre-DM, and steroid treatment of included study participants. It is important to know the demographic variables associated with post-COVID-19 DM development to predict the future prevalence of the disease and create proper prevention plans [1,11].

Physiological variables (lab tests)

The second subtheme presents physiological variables which include genetic and immunity markers, and diabetes-specified lab tests including the RBG level, the FBG level, the HbA1c level, the c-peptide level, the fasting c-peptide level, and the ketoacidosis status of included study participants. It is important to know the physiological variables associated with post-COVID-19 DM development according to the IDF and WHO classification which has been used as a framework to assess the criteria because this has implications for the treatment plan [1,11].

Theme 3: post-COVID-19 DM treatment

The third theme presents post-COVID-19-DM treatment that describes how different post-COVID-19 DM patients have been treated for DM. It is important to know the different treatment protocols that have been followed by the researchers with those who have developed DM post-COVID-19 infection because this has implications for their DM management and complications. Some researchers have used the early stages of the T2DM treatment protocol which includes lifestyle modification only to treat post-COVID-19 DM patients, despite knowing the fact that the variables/lab tests were not aligned with T2DM diagnosis [21].

Discussion:-

This integrative review led to a better understanding of the novel form of DM, post-COVID-19 DM, and explained the demographic and physiological variables that differentiate post-COVID-19 DM from the other types of DM. It suggests that post-COVID-19 DM could be considered a novel form of DM, however, many inconsistencies are

found in the existing literature regarding the nomenclature, the risk factors, demographic and physiological variables, and the treatment used to diagnose DM that has developed post-COVID-19 infection. More research studies are needed to classify it as T1DM, T2DM, LADA, or a more specific subtype [10].

Post-COVID-19 DM is suggested to be a unique type of DM because of its genetic and immunity markers. The literature analysis proved that all post-COVID-19 DM patients have a negative autoantibodies test (ICA and anti-GAD), similar to T2DM patients [14]. T1DM and LADA patients are characterized by having positive autoantibodies test (ICA and anti-GAD) [12]. On the other hand, T2DM patients are characterized by having negative HLA DR1-DR3-DQ2 genes [14]. The literature analysis evidenced that when the HLA DR1-DR3-DQ2 gene test was executed in post-COVID-19 DM patients, it was positive in all of them, similar to T1DM, and LADA patients [14]. The specific genetic characteristics of post-COVID-19 DM patients might imply the treatment. Like T1DM, gene transfer or gene expression could be used to normalize insulin production of post-COVID-19 DM patients in the future [22]. Hence, gene therapy could be suggested for post-COVID-19 DM patients in the future. Thus, post-COVID-19 DMwas considered a unique form of DM with its physiological features.

The IDF and WHO have strict protocols for treating and managing each type of DM [1,11]. One reason that highlights post-COVID-19 DM as a separate classification is how patients initially presented to the hospital with high blood glucose levels, ketoacidosis, and the need for initial insulin injection at the onset of post-COVID-19 DM and insulin dependency. The literature analysis proved that all post-COVID-19 DM patients present to the hospital with an urgent need for insulin injection, similar to T1DM patients [23]. Both T1DM and post-COVID-19 DM patients are admitted to the hospital with highly elevated blood glucose levels and ketoacidosis [23]. Thus, an immediate intravenous insulin infusion and fluid replacement are needed to resolve the hyperglycemic status [23]. Untreated hyperglycemia and ketoacidosis might lead to a hyperglycemic crisis, cell damage, and organ failure [23], 2015). LADA and T2DM patients do not need insulin injections at the onset of DM [12,24]. On the other hand, T1DM and LADA patients depend on insulin injections for the rest of their lives to manage DM[12,24]. T2DM patients do not need insulin injections except at the end stages of their disease [24]. Thus, lifestyle modification only or a mixture of lifestyle modification and antihyperglycemic pharmacotherapeutic agents is enough for T2DM management [24]. This literature analysis verified that after hospital discharge, some post-COVID-19 DM patients depend on insulin injections, and some do not need it, like T2DM patients. For both T2DM and post-COVID-19 DM, some patients can manage their DM without insulin[24]. Taking into consideration that more long-term studies are needed with a longer follow-up to determine their future need for insulin injection in addition to the importance of diabetes patient education for COVID-19 patients and post-COVID-19 infection.

The treatment protocol used to manage post-COVID-19 DM long-term after being discharged from the hospital was inconsistent among patients with a mixture of the different treatment protocols used for the different types of DM. Similar to the T1DM treatment protocol, some post-COVID-19 DM patients continued to require subcutaneous insulin injections after hospital discharge [23]. Individuals who are diagnosed with T1DM are required to take subcutaneous insulin injections for their entire life [23]. However, similar to T2DM, the treatment protocol for post-hospital discharge uses anti-hyperglycemic medications and lifestyle modification or lifestyle modification only for DM management [24]. This protocol has been used with some post-COVID-19 DM patients and helped them to manage their DM properly [21,25].These characteristics make post-COVID-19 DM might be considered a unique type of DM that needs a specific treatment protocol different than the existing known DM treatment protocols. Having an exact classification for post-COVID-19 DM is important because it will have implications for the treatment protocol, which will be followed by post-COVID-19 DM patients [1,11]. Further work is integral for a better understanding of this novel form of DM. Optimizing management plans is also needed to improve patients' outcomes.

Conclusion:-

In conclusion, the findings of this integrative review provided an important insight into post-COVID-19 DM classification and treatment by other researchers compared with the other types of DM recognized by the IDF and the WHO. This integrative review highlighted that post-COVID-19 DM might be considered a novel form of DM with unique genetic features. It emphasized the importance of Diabetes Education post-COVID-19 infection and underlined that post-COVID-19 DM might need a unique treatment protocol. This integrative review called attention to the need for further research on post-COVID-19 DM.

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