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RESEARCH ARTICLE

CONSANGUINITY AS A SIGNIFICANT RISK FACTOR FOR DIABETES MELLITUS: A SYSTEMATIC REVIEW

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Abstract

Objectives: This systematic review aims to study the recent updates regarding the association between consanguinity and DM.
Methods: PubMed, SCOPUS, Web of Science, and Science Direct were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process.
Results& interpretation: Our results included ten studies with a total of 8878 patients, and 4565 (51.4%) were males. Eight studies included patients with T2D, and two included T1D. The prevalence of consanguinity ranged from 21.9% to 95% in T2D and 70.8% in T1D.PreoperThe development of T2D was significantly influenced by consanguinity, consanguineous marriages, and maternal diabetes, particularly in developing Arab countries where the prevalence of T2D in families is very high. Significant risk variables for T2D in MetS patients were consanguineous marriages, maternal aunts, maternal grandpas, and the presence of MetS in the parent's family. A family history of autoimmune disease in children or paternal consanguinity is not strongly associated with the complexity of T1D.

Introduction:-

Diabetes mellitus (DM) is a metabolic illness with diverse aetiologies that is characterised by persistent hyperglycemia as well as abnormalities in the metabolism of carbohydrates, fats, and proteins. It is brought on by flaws in either insulin action (resistance) or insulin secretion [1]. The shift from communicable to non-communicable diseases occurred shortly after the demographic shift and caused a significant change in the way we think about health and illness [2].

Similar trends have been observed in other developing nations, where demographic and epidemiologic shifts have occurred considerably more quickly than expected. The diabetes pandemic is a prime example; in 2000, there were an estimated 171 million diabetic patients globally. This number is forecast to rise to 366 million by 2030, and the proportion of diabetics living in developing nations is predicted to rise from 74% to 81% by that same year [3].

Type 1 diabetes (T1D) is becoming increasingly common at a rate of 3% to 5% each year, which shows that during the previous 60 or more years, significant environmental exposure has altered due to either the progressive addition of a susceptibility factor or the removal of a protection factor. T1D outbreaks and seasonality may point to an

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infectious atiology, which may be connected to improving cleanliness and a decline in herd immunity. Environmental pollutants and food during early childhood are also important[4].

Given that the incidence of islet autoimmunity rises in the second year of life, prenatal and immediate post-natal exposures seem crucial. Enteroviral infections are the infectious agents that have attracted the most attention. Large prospective investigations, including a significant randomized clinical trial, did not confirm early indications that exposure to cow's milk was a factor in the onset of islet autoimmunity. Although multiple studies have linked various aspects of early childhood food and viral exposures to 1.5–2–fold increases in the likelihood of islet autoimmunity or T1D, none of the connections appear especially significant or universal across distinct cultures [4].

Over the past few decades, Type 2 diabetes (T2D) prevalence has been rising quickly around the globe [5]. According to IDF projections from 2017, there were 451 million adults worldwide who had diabetes, and by 2045, that number is expected to rise to 693 million [6]. A progressive decrease in insulin secretion causes T2D, which is frequently accompanied by varying degrees of insulin resistance [7, 8]. Age, ethnicity, family history, low socioeconomic position, obesity, metabolic syndrome, and bad lifestyle choices are just a few of the risk variables linked to the pathogenesis of T2D [5, 7, 9]. These T2D risk variables interact with one another in a convoluted pathophysiologic process with underlying gene-environment interactions that appear to vary among cultures [5, 9, 10]. This systematic review aims tostudythe recent updates regarding the association between consanguinity and DM.

Methodology:-

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in conducting this systematic review [11].

Study Design and Duration

October 2023 marked the start of this systematic review.

Search strategy

To discover the pertinent literature, a thorough search was conducted across four main databases: PubMed, SCOPUS, Web of Science, and Science Direct. We limited our search to English and considered each database's specific needs. The following keywords were transformed into PubMed Mesh terms and used to locate the pertinent studies; "Diabetes mellitus," "Type 1 diabetes," "Type 2 diabetes," "Consanguinity," "Family history," "Consanguineous marriages," and "Risk Factors," The Boolean operators "OR" and "AND" matched the required keywords. Publications with full English text, available free articles, and human trials were among the search results.

Selection criteria

Inclusion criteria

We considered the following criteria for inclusion in this review:

1. Study designs that investigated the recent updates regarding the association between consanguinity and DM.
2. Studies conducted between 2013 and 2023.
3. No age limits were restricted.
4. Only human subjects.
5. English language.
6. Free accessible articles.

Exclusion criteria

We considered the following criteria for exclusion in this review:

1. Gestational diabetes.
2. Diabetic patients associated with other syndromes or neurological disorders (e.g. Friedreich's ataxia, Huntington's disease, and severe obesity syndromes like Bardet-Biedl and Prader-Willi).
3. Genetic variants.

Data extraction

The search technique's output was double-checked using Rayyan (QCRI) [12]. By modifying the combined search results with a set of inclusion/exclusion criteria, the researchers evaluated the relevance of the titles and abstracts.

Each paper that met the requirements for inclusion underwent a careful examination by the reviewers. The authors talked about methods for resolving disputes. The approved study was uploaded using a data extraction form already created.The authors extracted data about the study titles, authors, study year, country, participants, gender, type of diabetes, prevalence of consanguinity, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for data synthesis

Utilizing information from pertinent research, summary tables were made to offer a qualitative evaluation of the findings and study elements. The most effective method for using the data from the included study articles was selected after the data for the systematic review were retrieved.

Risk of bias assessment

The ROBINS-I risk of bias assessment technique for non-randomized trials of therapies was used to evaluate the caliber of the included studies [13]. The seven themes that were assessed were confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choice of the reported result.

Results:-

Search results

A total of 566 study articles resulted from the systematic search, and 201 duplicates were deleted. Title and abstract screening were conducted on 365 studies, and 298 were excluded. 67 reports were sought for retrieval, and 4 articleswere retrieved. Finally, 63 studies were screened for full-text assessment; 41 were excluded for wrong study outcomes, 10 for the wrong population type, and 2 articleswere letters to the editors. Ten eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1.**

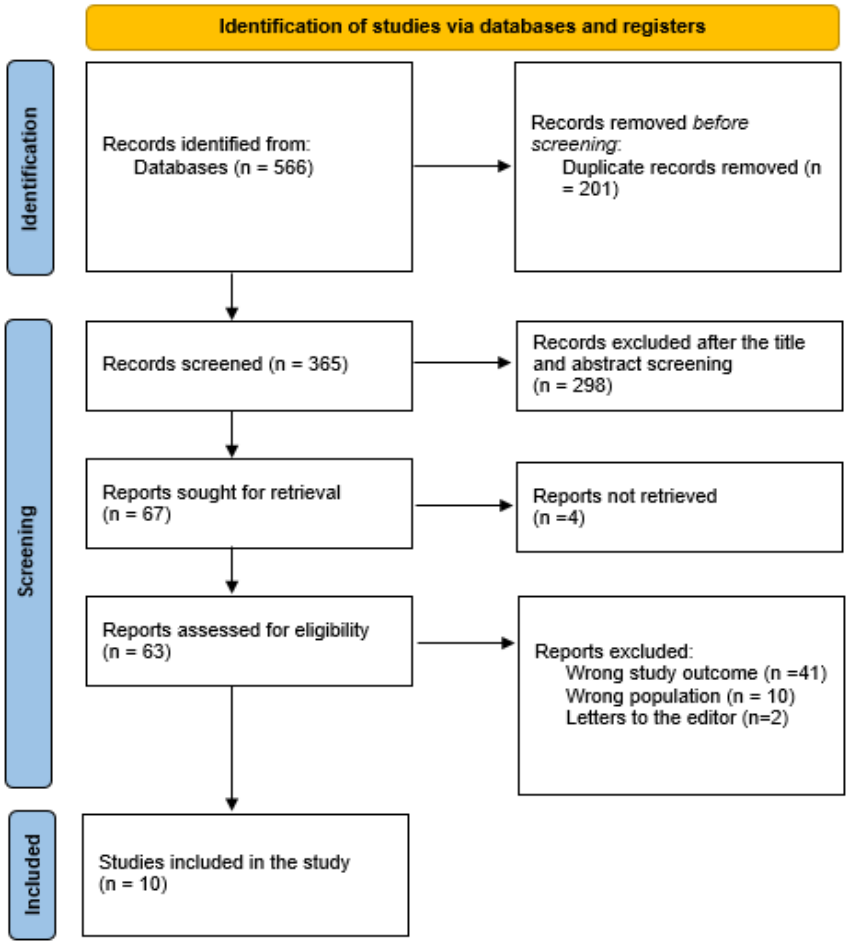

Figure (1):- PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included ten studies with a total of 8878 patients, and 4565 (51.4%) were males. Five articles were case-control studies [14, 16, 18, 22 23], three were cross-sectional [15, 17, 19], one was retrospective in nature [20], and one was cohort [21]. Four studies were conducted in Qatar [17-19, 21], three in Saudi Arabia [13, 16, 22], one in Oman [15], and one in Iran [23].

Table (2) presents the clinical characteristics. Eight studies included patients with T2D [14, 21], and two included T1D [22, 23]. The prevalence of consanguinity ranged from 21.9% [14] to 95% [15] in T2D and 70.8% in T1D. Consanguinity, consanguineous marriages, and maternal diabetes played a crucial role in developing T2D, especially in developing Arab countries where there are very high familial aggregations of T2D. One study reported that parental family history of MetS, maternal aunt, maternal grandpa, and consanguineous marriages among MetS patients was a significant risk factor for T2D development [19]. Consanguinity did not significantly impact the likelihood of developing diabetes in one study [18]. The development of T1D in children was not strongly correlated with parental consanguinity or a family history of autoimmune disease, proving that T1D is a complex illness [22, 23].

Study	Study design	Country	Participants	Mean age (years)	Males (%)
Alzahrani et al., 2021 [14]	Case-control	Saudi Arabia	481	57.8 ± 11.6	164 (43.1)
Al-Sinani et al., 2014 [15]	Cross sectional	Oman	234	53 ± 10	116 (50%)
Gosadi et al., 2014 [16]	Case-control	Saudi Arabia	362	45.84±8.9	362 (100)
Bener&Al-Hamaq 2016 [17]	Cross sectional	Qatar	2717	45.5±14	1394 (51.3)
Christos et al., 2015 [18]	Case-control	Qatar	801	27 ± 5.9	384 (47.9)
Bener et al., 2014 [19]	Cross sectional	Qatar	1552	45.7 ± 11.2	758 (48.8)
Aravinda et al., 2019 [20]	Retrospective	India	519	53.3	289 (55.7)
Multu et al., 2014 [21]	Cohort	Qatar	1705	45.6 ± 14.2	862 (50.6)
Albishi et al., 2022 [22]	Case-control	Saudi Arabia	380	6.30 ± 3.07	173 (45.5)
Yaghootkar et al., 2019 [23]	Case-control	Iran	127	2 to 4	63 (49.6)

Table (2):- Clinical characteristics and outcomes of the included studies.

Study	Diabetes type	Prevalence of consanguinity	Main outcomes	ROBIN-I
Alzahrani et al., 2021 [14]	T2D	32 (21.9%)	Consanguinity is associated with an increased risk of T2D in the Saudi population. This association may influence the higher risk of DM prevalence.	Moderate
Al-Sinani et al., 2014 [15]	T2D	223 (95)	The results of this investigation support the Omani population's family aggregation of diabetes. Omanis have a very high familial aggregation of T2D compared to other populations. This may be because Omanis have a very high consanguinity rate. Given that practically everyone appears to have a genetic propensity to diabetes, the substantial lifestyle changes of the past 25 years may have contributed to the rise of T2D in the community.	Moderate
Gosadi et al., 2014 [16]	T2D	NM	Consanguinity may raise the risk of T2D by hastening the start of the condition and amplifying any genetic influences on FBG.	High

Bener&Al-Hamaq 2016 [17]	T2D	796 (29.3)	The prevalence of diabetes in Qatar is far higher than the IDF estimates suggest; based on these estimates, Qatar should rank among the top 10 countries worldwide for diabetes prevalence. A family history of the disease may also cause the current diabetes epidemic, consanguinity marriages, inherited gene-environment interactions, inadequate nutrition in utero and early life, and excessive nutrition in later life.	Moderate
Christos et al., 2015 [18]	T2D	NM	Consanguinity did not significantly impact the likelihood of developing diabetes (unadjusted OR = 1.5; 95% CI = 0.8-2.8; p = 0.21). With a contribution that transcends genetic risk factors, demographic and lifestyle variables appear to be the primary risk factors for the high DM levels in Qatar.	Moderate
Bener et al., 2014 [19]	T2D	NM	T2D development in Qatar is substantially correlated with parental family history of MetS, maternal aunt, maternal grandpa, and consanguineous marriages among MetS patients. These findings confirm the need for earlier T2D screening in MetS patients with a positive MetS family history.	Moderate
Aravinda et al., 2019 [20]	T2D	308 (59.34)	When family members of T2D patients are screened, risk factors like obesity, FH (maternal history of T2D), and consanguinity may besignificant variables. Early management and a lower risk of complications may result from this screening. Additionally, the susceptible population can receive counseling for managingT2D, which includes routine blood glucose testing and lifestyle modifications.	High
Multu et al., 2014 [21]	T2D	NM	The prevalence of diabetes in Qatar is far higher than what the IDF estimates show; these estimates place Qatar among the top ten countries in the world for diabetes prevalence. The current diabetes epidemic in Qatar's Arab populations may also be caused by a family history of the disease, consanguinity marriages, inherited gene-environment interactions, inadequate nutrition in utero and in early life, as well as excessive nutrition in later life.	Moderate
Albishi et al., 2022 [22]	T1D	269 (70.8)	The development of T1D in children was not strongly correlated with parental consanguinity or a family history of autoimmune disease, proving that T1D is a complex illness. T1D risk is boosted by a history of afflicted first-cousin parents.	Moderate
Yaghootkar et al., 2019 [23]	T1D	NM	In an Iranian community with a high proportion of consanguineous unions, the T1D genetic risk score can be utilised to differentiate between monogenic and T1D. With the use of genetic testing, this test can help identify kids who are more likely to develop monogenic diabetes. Identifying these patients would lower treatment costs and enhance clinical course management.	High

Discussion:-

National and international organizations currently support a number of clinical practice guidelines for T2D screening and prevention [24]. In light of this, in clinical practice, adult patients are routinely tested for prediabetes and T2D using predetermined screening criteria relating to recognized T2D risk factors, such as those advised by the American Diabetes Association [8]. This study reported that consanguinity, consanguineous marriages, and maternal

diabetes played a crucial role in developing T2D, especially in developing Arab countries where there are very high familial aggregations of T2D. Significant data has accumulated on the rise in diabetes prevalence in developed nations [25, 26]. Long duration, slow progression, and early mortality from all causes, notably coronary heart disease, are traits of T2D [9]. Patients who have diabetes use the healthcare system more frequently and for longer periods of time than those who do not [27]. Additionally, diabetes and its effects limit productivity in patients, lowering their quality of life [17, 27, 28]. Contrary to wealthy nations, developing nations such as Qatar lack data on diabetes economic costs and future estimates.Target behavioral changes that may be able to postpone the onset of disease and enhance health outcomes. According to **Harrison et al.** [29], family history data may be helpful for promoting public health because it reflects both genetic and environmental influences.

Parental family history of MetS, maternal aunt, maternal grandpa, and consanguineous marriages among MetS patients was a significant risk factor for T2D development in this review [19].Age, race, weight, women's menopause, smoking, low income and socioeconomic status, high carbohydrate intake, cigarette smoking, low physical activity, soft drink consumption, antipsychotic medication, T2D, poor cardiovascular fitness, and genetic factors are just a few of the factors that may contribute to the development of the metabolic syndrome [30-32]. According to estimates, overweight and obesity are responsible for about 58% of T2D worldwide, and weight gain is to blame for 90% of T2D in Western nations [33].**Meigset al.'s** earlier study[34] found that regardless of BMI status, persons with MetS or insulin resistance had a greater chance of developing diabetes than those who were overweight or obese without the condition. Additionally, compared to those of normal weight who did not have insulin resistance, obese participants had a threefold higher chance of developing diabetes, whereas overweight ones did not. In addition, MetS is more likely to strike a child of parents with the condition. This is supported by research showing that up to 50% of variation in MetS characteristics in offspring may be attributed to hereditary factors [29, 35-37].

The understanding of behavioral and lifestyle risk factors for T2D has improved as a result of prospective studies [38]. However, there is significant individual diversity in responsiveness to risk factor therapies, which is probably caused by variations in T2D risk associated with behavior, physiology, and genetics [39]. Therefore, future development of focused T2D prevention measures may benefit from an increased understanding of the connections between genes and the environment. Novel biomarkers and intermediate states linked to diabetes risk also present a possibility for early detection of diabetes risk [40].Although there is no known cure for T2D at this time, the disease's onset may be postponed in many at-risk people and prevented in some of them by early detection of metabolic risk factors and intervention in the disease's progression through modification of behavioral and lifestyle risk factors. With a long-term goal of tackling this significant public health issue, continued work to better understand T2D risk may help in the creation of ideal solutions for T2D prevention.

The development of T1D in children was not strongly correlated with parental consanguinity or a family history of autoimmune disease, proving that T1D is a complex illness [22, 23].The risk is elevated to approximately 1 in 40 in children of mothers with T1D and to 1 in 15 in children of T1D-affected fathers; the cause of this difference may be epigenetic in nature. Siblings of people with T1D are at risk at a rate of 1 in 12 to 1 in 35 [41]. Siblings of patients diagnosed at age 7 years are at a noticeably higher risk than those diagnosed later [42]. Monozygotic twins have a rate of up to 1 in 3 [43]. The probability of having a child with T1D is 2.6% by the age of 40 and is much higher in fathers (3.6%) than in mothers (1.7%) [42].10% of first-degree relatives are predicted to have type 1 diabetes by the age of 60 [43]. Less than 10% of T1D cases in the general population are "familial," but neither the frequency of the HLA-DR,DQ gene nor the incidence of islet autoantibodies distinguishes "familial" cases from "sporadic" ones [44].

Conclusion:-

Maternal diabetes, consanguineous marriages, and consanguinity all had a significant influence on the development of T2D, particularly in developing Arab nations where the prevalence of T2D in families is very high.Consanguineous marriages, maternal aunts, maternal grandpas, and MetS in the parent's family were all significant risk factors for T2D in MetS patients.T1D is a complex disorder that is not highly connected with parental consanguinity or a family history of autoimmune disease in children.

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