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REVIEW

Review of Genetic and Artificial Intelligence approaches to improving Gestational Diabetes Mellitus Screening and Diagnosis in sub-Saharan Africa

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Background: Adverse outcomes from gestational diabetes mellitus (GDM) in the mother and newborn are well established. Genetic variants may predict GDM and Artificial Intelligence (AI) can potentially assist with improved screening and early identification in lower resource settings. There is limited information on genetic variants associated with GDM in sub-Saharan Africa and the implementation of AI in GDM screening in sub-Saharan Africa is largely unknown. **Methods**: We reviewed the literature on what is known about genetic predictors of GDM in sub-Saharan African women. We searched PubMed and Google Scholar for single nucleotide polymorphisms (SNPs) involved in GDM predisposition in a sub-Saharan African population. We report on barriers that limit the implementation of AI that could assist with GDM screening and offer possible solutions. **Results**: In a Black South African cohort, the minor allele of the SNP rs4581569 existing in the PDX1 gene was significantly associated with GDM. We were not able to find any published literature on the implementation of AI to identify women at risk of GDM before second trimester of pregnancy in sub-Saharan Africa. Barriers to successful integration of AI into healthcare systems are broad but solutions exist. **Conclusions**: More research is needed to identify SNPs associated with GDM in sub-Saharan Africa. The implementation of AI and its applications in the field of healthcare in the sub-Saharan African region is a significant opportunity to positively impact early identification of GDM.

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Abbreviations: AI, Artificial Intelligence; ADHD, Attention Deficit-Hyperactivity Disorder; ANN, Artificial Neural Network; AUC, Area Under the Receiver Operating Characteristic Curve; BMI, Body Mass Index; CKD, Chronic Kidney Disease; CVD, Cardiovascular Disease; DL, Deep Learning; EHR, Electronic Health Records; EMR, Electronic Medical Records; ESKD, End-stage Kidney Disease; GDM, Gestational Diabetes Mellitus; GWAS, Genome Wide Association Studies; IDF, International Diabetes Foundation; IRB, Institutional Review Board; LDL, Low-density Lipoprotein; LMIC, Low- and Middle-Income Countries; ML, Machine Learning; NGO, Non-Governmental Organization; NGS, Next-generation Sequencing; OGTT, Oral Glucose Tolerance Test; PDX1, Pancreatic and Duodenal Homeobox 1; SNP, Single Nucleotide Polymorphisms; T2DM, Type 2 Diabetes Mellitus.

Keywords: Artificial Intelligence, Genetic Variants, Gestational Diabetes Mellitus, sub-Saharan Africa

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INTRODUCTION

The American Diabetes Association defines Gestational Diabetes Mellitus (GDM) as "any degree of glucose intolerance with onset or first recognition during pregnancy" [1]. In 2021, the estimated prevalence of GDM in Africa, according to the International Diabetes Foundation (IDF), was 13% [2]. In low- and middle-income countries (LMIC), the World Health Organization (WHO) reported that an estimated 990 women die every day from pregnancy related causes that are preventable [3]. Many of the gestational diabetic related deaths in women result from barriers that exist in healthcare systems of sub-Saharan African countries due to a variety of factors such as quality of care, limited trained professionals, and under-resourced infrastructure of hospitals [4]. Furthermore, the treatment of GDM, assuming 100% efficacy, can be as high as $3555 USD [5]. Diabetes-related health expenditure per person in African countries in 2021 was $547 USD on average [2]. This suggests that the consequences of developing GDM during pregnancy goes beyond severe health effects on prenatal and neonatal development but is also a massive economic burden. Genetic predictors can help us better understand predisposition to GDM during pregnancy, potentially pave the way for future research, and catalyze the development of a more cost-effective method of diagnosing and treating GDM.

AI has been described as the "science and engineering of making intelligent machines" [6]. In healthcare especially, AI is continuously being adopted by healthcare organizations to aid in the process of diagnosis and identification of individuals at risk. Current applications of AI revolve around supervised learning and the training of Machine Learning (ML) and Deep Learning (DL) algorithms, such as neural networks, to a training dataset comprising of multiple factors: electronic health records, patient demographics, medical notes on treatment and diagnosis, and many more [7,8]. Once training of the algorithms is completed, they are tested based on metrics, such as area under the receiver operating characteristic curve (AUC) and F1 score (harmonic mean of precision and recall), on the remaining, unseen portion of the dataset, and algorithms further hyperparameter tuned (process of tweaking variables existing in the algorithm) for the best outcome [9]. Criticality of variables and feature importance is then identified to understand patterns between existing factors and the condition of interest.

Health Issues Associated with GDM in Mothers and Infants

Currently, GDM poses a severe health risk for both the mother and the fetus. GDM can be associated with psychological conditions such as antenatal depression, with one study stating that 20% of women who had GDM had significant symptoms of depression [10]. The condition is also associated with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) [11]. Women with GDM face an increased risk of adverse perinatal outcomes like preterm birth and respiratory distress [12]. Some of the long-term complications associated with preterm birth are increased risk for conditions such as Attention Deficit-Hyperactivity Disorder (ADHD) and learning difficulties due to behavioral issues [13]. Prior pregnancies with GDM have also been associated with an increased risk of cardiovascular disease (CVD) and associated risks such as hypertension, higher LDL, and non-LDL cholesterol levels [14]. GDM is associated with developing Type 2 Diabetes Mellitus (T2DM). One study showed that women who have had GDM during pregnancy are up to 7 times more likely to develop T2DM [15]. Of women who had GDM in prior pregnancies, the recurrence rate of the condition is 52% with women going on to develop a more severe case of GDM [16].

GDM also has serious short-term and long-term impacts on fetal development. GDM is highly associated with fetal macrosomia, a condition diagnosed to a fetus with a birth weight greater than 4000g, which increases the risk of shoulder dystocia and has been seen to increase the rate of admission to the neonatal intensive care unit and the rate of cesarean section [17,18]. If GDM is undiagnosed and not managed, as a result, hypoglycemia can arise in infants [19].

Current significant risk factors associated with GDM are a high BMI, family history of diabetes mellitus (DM), and older age [20,21]. Many studies have also identified a correlation with individuals of certain ethnicities being more predisposed to GDM. In one study, conducted in the Netherlands, women of Ghanaian or any other sub-Saharan African ethnicity were at higher risk of developing GDM during pregnancy than the Dutch [22]. Although these risk factors serve as a model to understand whether an individual is at risk of developing GDM, researchers have shown that screening methods using these risk factors were poor predictors for this condition. A study completed at the Helsinki University Central Hospital in Finland showed that 47% of women with GDM would have gone undiagnosed using the current risk-factor screening strategy [23]. To diagnose GDM, physicians administer the oral glucose tolerance test (OGTT) during the second trimester of pregnancy, occurring from week 14 to week 28. By this time, the women and fetuses will have already suffered from adverse health effects of the condition [24]. This is where genetic predictors of GDM may fill this gap in identifying individuals at high risk of developing the condition during pregnancy early on.

Table 1. Barriers, Potential Solutions, and Impact of AI in Clinical Health in sub-Saharan Africa

Problem	Solution	Impact
Lack of awareness and education on AI and its use cases in the field of healthcare.	• Employ subject matter experts in data science on ethics institutional review boards to provide insights into data & computational related studies. • Introduce youth to AI at a grassroot level. • Encourage companies with AI expertise in health to set up sites in different sub-Saharan African countries. • Integrate courses such as data science, computational biology, biostatistics, bioinformatics and genomics into sub-Saharan African educational institutions.	This would accelerate the process of launching more studies around AI and would pave the way for more research into conditions like GDM from a technological standpoint.
Limited access to large sub-Saharan African clinical dataset due to poor infrastructure and the absence of centralized database systems.	• Develop country-wide systems where clinicians and physicians can store patient related data in Electronic Medical Records. • Governments sponsorship of public hospitals through effective data storage mechanisms.	Widespread implementation of database systems will provide researchers and clinicians with more data to deploy ML and AI technology to better capture Africa's diversity to allow scientists to understand specific ethnic and/or tribal groups that are at risk of developing certain conditions.
Insufficient legislation regarding data privacy laws and implementation of AI in healthcare services.	• Governments collaborate and learn from other countries where AI is being integrated into healthcare systems.	This will reduce chances of unethical AI algorithms being developed and will allow governments to regulate how AI is being implemented in hospital services and that datasets are representative of Africa's ethnic diversity.
Poor infrastructure and lack of funding.	• Through "political will", the commitment of political leaders and bureaucrats to undertake actions to achieve a set of objectives and to sustain the costs of those actions over time, governments fund studies and research and adopt AI in healthcare systems [49]. • Governments partner with NGOs that will provide better hardware to hospitals and healthcare providers.	With adequate funding and better infrastructure, hospital services will be able to effectively use AI as part of their diagnostic processes.

Genetic Predictors of GDM

According to investigators, the implementation of genetics and their studies in GDM "has significantly lagged behind that of other forms of diabetes" even though the condition has been proved to have some shared components of genetic architecture with T2DM [25-27]. Like T2DM, GDM is also identified through insulin resistance [28]. In addition, with family history of T2DM being a significant risk factor to developing GDM, it can be hypothesized that there are genes that are not only associated with developing T2DM but also GDM. Women of Latina, African American, Japanese, and Asian background had a recurrence rate of GDM that was greater than 50% serving to suggest that women of particular ethnicities may be greater genetically disposed to the condition [29]. A major reason why women of sub-Saharan African origin are not explicitly shown to be at higher risk of GDM is due to the lack of genetic testing done in countries in this region.

In a systematic review of GDM prevalence in Africa, investigators reported that only six countries in Africa (11% of the continent) recorded prevalence rates of GDM showing the lack of research in this area [30].We sought to review what is known about genetic predictors of GDM in sub-Saharan African women, highlight current barriers that limit the implementation of AI that could assist with GDM screening and offer possible solutions.

METHODS

We searched on databases PubMed and Google Scholar, using the search terms "genetic variants sub-Saharan Africa GDM," "genetic variants GDM Africa," "genetic variants of GDM in sub-Saharan Africa," "genetic variants sub-Saharan Africa gestational diabetes," "hyperglycemia pregnancy sub-saharan africa genetic variants," "hyperglycemia pregnancy africa genetic variants." We reviewed articles for implementation of AI in GDM screening and outline barriers to the integration of AI into healthcare systems in sub-Saharan Africa, possible solutions and their impact.

RESULTS

There was only one article that investigated genetic factors for GDM in sub-Saharan Africa. The study, conducted on a Black South African cohort, showed, after adjustment for BMI and age, the minor allele of the SNP rs4581569 existing in the PDX1 gene was significantly associated with GDM [31]. We were not able to find any published literature on the implementation of AI to identify women at risk of GDM before second trimester of pregnancy in sub-Saharan Africa. Based on our review of the literature, we outline the major barriers to integration of AI into healthcare systems in sub-Saharan Africa, possible solutions, and the broader potential impact (Table 1).

DISCUSSION

Further studies are needed to fully examine and discover genetic variants involved in elevating the risk of GDM, specifically in sub-Saharan Africa. However, this may be difficult to pursue due to a variety of socio-economic factors involving genetics, namely price of genetic testing, stress on healthcare systems and limited knowledge about genetic screening. Since January 2019, Africans have only represented 3% of the population in the genome wide association studies (GWAS), and this has dropped to 1.1% in 2021 due to several barriers affecting the involvement of genetic research in the continent [32]. One of these barriers is affordability and price of genetic testing. With the prevalence of health insurance coverage being particularly low in the region (10.6% of females and 14% of males) and national health insurance not covering the full cost of the screening, under-resourced individuals do not see the need to uptake an additional financial burden for genetic testing [33,34]. Even though the cost of genetic testing is declining with the introduction of next-generation sequencing (NGS) technologies, that can sequence the whole human genome for less than $1000 USD, due to the high-cost process of importing reagents and the servicing of machinery and equipment, many sub-Saharan African facilities are unable to provide affordable testing services for these individuals [34,35].

Another key barrier to genetic service delivery in sub-Saharan Africa is education and the lack of practical implementation of genetics. A study conducted in Kenya showed that health personnel lacked the practical knowledge of interpreting genetic tests, while having completed university level courses in genetics [36]. This situation is further exacerbated by the fact that engagement of government policy makers is minimal, leading to lack of funding for studies and a scarcity of legislation [37,38]. As a result, facilities rely on inadequate funds from academic bodies resulting in studies that have too low of a sample size to make valid and justifiable conclusions for an entire population, or facilities cannot complete the study due to cost of manpower [34]. In addition, due to a shortage of skilled health workers, pregnant women are unlikely to receive sufficient treatment [39]. However, a possible long-term solution may revolve around the implementation of Artificial Intelligence (AI) driven technology in healthcare systems in sub-Saharan Africa with using genetic screening to understand specific populations at risk.

Using AI coupled with clinical variables, healthcare providers may be able to identify women that are at risk of developing GDM prior to clinical presentation. For example, in a study conducted in Mexico, investigators developed an AI model to predict the development of GDM in Mexican women using predictive variables for GDM such as family history of T2DM, pregestational body mass index, and more. The study's most effective algorithm, an Artificial Neural Network (ANN), produced an AUC, sensitivity, and specificity of 0.8471, 83.26%, and 70.28%, respectively [40]. A meta-analysis of pooled studies of ML prediction models for GDM also showed that such approaches are high performing in identifying patients with GDM and are a more cost-effective screening method for the condition, but still lack accounts for internal biases of the model and that feature selection methods should be decided based on clinical need rather than optimizing accuracy [41].

The most obvious barrier of AI implementation to predict GDM in sub-Saharan Africa is the limited access physicians and researchers have to large clinical datasets, and in particular data with labels that require medical expert notes and analysis [42]. Furthermore, due to a low level of adoption of EHRs (Electronic Health Records) and EMRs (Electronic Medical Records), with rates being as low as 15% in low-income countries, in specifically Francophone countries of sub-Saharan Africa, digitizing healthcare is slow [43,44]. This may result in the introduction of AI technologies that were trained on non-sub-Saharan African populations resulting in both algorithmic racial and ethnic biases that could increase misdiagnoses and the unequal distribution of healthcare resources to underrepresented minority groups [45]. This is also showcased in the wide disparity in utilization of digital healthcare solutions such as mobile health where less than 50% of sub-Saharan African countries fully incorporate the platform into their healthcare systems [46-48].

With regards to GDM, if an effective AI-driven approach can be used to identify women predisposed to the condition coupled with thorough work on genetic variants to understand certain ethnic groups that are at elevated risk, it is not inconceivable that women in sub-Saharan Africa could receive a higher standard of care that is comparable to women across the globe.

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