**وه‌زاره‌تی خوێندنی باڵا و تۆێژینه‌وه‌ی زانستی**

 **Ministry of Higher Education &**

 **Scientific Research**

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| **PhD Research Proposal** |
| 1. **Title of PhD research proposal:**

**Vitamin D deficiency in prediabetic patients- a modifiable risk factor of T2D development in Kurdistan region-Iraq** |
| **2. General information**  |
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| **2. Summary (Abstract) of PhD research proposal**  The incidence of Diabetes and vitamin D deficiency have been increasing in Kurdistan region in similar a pattern as worldwide while this topic of research gained less attention in comparing to cancer research.Therefore, the current proposal aims to better characterize the Vitamin D status in diabetic and prediabetic patients in Kurdistan region in accordance to internationally recognized standards which consists of three main objectives as organized in the following; In the first aim, the prevalence/incidence of Vitamin D deficiency among diabetic and prediabetic patients in Kurdistan region will be determined. To this end, as one of the most reliable standards worldwide, criteria and guidelines of American Diabetes Association (ADA) for prediabetes will be employed.*In the second aim we will try to answer this question; Does Vitamin D deficiency predispose prediabetic patients to develop T2D earlier?* For this aim, eligible prediabetic cohort will be categorized based on the status of Vitamin D (normal, low, severely deficient).*In the third aim we will find the answer to this question; Does Vitamin D supplementation delay and/or prevent the onset of diabetes in prediabetic patients?* |
| **3. Introduction**Diabetes, the leading cause of death in developed countries, is a metabolic disease characterized by the loss of glucose homeostasis due to defective insulin function and/or insulin secretion. The prevalence of diabetes is rising dramatically and affecting up to 385 million people all over the world, among them Type 1 Diabetes (T1D) accounts for approximately 10% and a large proportion belongs to the Type 2 Diabetes (T2D)(1; 2). It is predicted that the number of people with T2D will increase from 451 million, as estimated in 2017, to 693 million by 2045 (3) (3; 4). In the long term, the diabetic condition can cause several serious complications such as cardiovascular diseases, renal failure and neural damage (5). Type 2 diabetes accounts for more than 90% of all cases of diabetes which became a global crisis, particularly in developing countries. There are many factors that have been attributed to the rising epidemic of T2D like; increased economic growth and urbanization, lack of physical activity and unhealthy diets, and population aging (6-8). Under normal physiological conditions, when the blood glucose level is elevated, e.g., during post-feeding, pancreatic β-cells detect and release insulin into the bloodstream to enhance glucose uptake and storage by the peripheral tissues. However, several risk factors such as age, obesity, and inflammation may prolong the hyperglycemic state due to insulin resistance of peripheral tissues (9-15).Like T2D, Vitamin D deficiency became more prevalent worldwide in last couple decades (16; 17). Interestingly, both share common risk factors like physical inactivity, aging, and obesity (18; 19). In recent years, Vitamin D supplementation gained more attention as a potential strategy for preventing /ameliorating different pathophysiological conditions (20-28) because of its effects on calcium hemostasis, immunoregulation, inflammation, insulin secretion and action (17-19; 29-35). Observational studies (association/correlation) and experimental investigations (molecular mechanisms) suggest the beneficial effects of Vitamin D. However, these results didn’t establish yet a clear causal/effect link.  |
| **4. Research objectives**1. Estimate the prevalence of diabetics in Kurdistan Region/Iraq.
2. The prevalence/incidence of Vitamin D deficiency among diabetic and prediabetic patients in Kurdistan region will be determined.
3. Does Vitamin D deficiency predispose prediabetic patients to develop T2D earlier?
4. Does vitamin D supplementation delay and or/ prevent the onset of diabetes in prediabetes in prediabetic patients?
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| **5. Methodology and data collection****1. Study Design and Cases**: In collaboration with Ministry of Health, data from Diabetes Centers in Erbil, Duhok, and Sulaimani will collected. A homogenous cohort (male and female, 25-65 years) of Vitamin D deficient of prediabetes will be recruited for the randomized, placebo-controlled trial after obtaining informed consent from participant and approval of Ethic Committee Board.Participants: (160) personsPrediabetes with Vit. D deficient prediabetic cohort will be categorized based on the status of Vitamin D levels (normal, low, and severely deficient).**2. Materials:**2.1 Reagents: include Biochemical reagents;2.2 Molecular kits include;miRNeasy Mini Kit (QIAGEN, Hilden, Germany).miRNA Retrotranscription and PreamplificationTaqMan MicroRNA Reverse Transcription Kit (Life Technologies, Carlsbad, CA, USA).2.3 Instruments;1. Enzyme linked immunosorbent assay (ELISA) method.2. Quantitative Real-Time PCR (qRT-PCR).**3. Anthropometric and Laboratory Assessment****3.1 Anthropometric measurements includes;**(Age, Gender, Body mass index BMI, Waist Circumference)**3.2 Diabetes-related parameters:** 1. Fasting Blood glucose (FPG)
2. Glycated hemoglobin Hb A1c
3. Β-cell function (serum insulin level) will evaluate by ELISA
4. Insulin secretion (Insulin sensitivity)
5. Insulin resistance (IR) will evaluate by the homeostasis model assessment of IR (HOMA-IR)= (Fasting insulin µIU/mL)X(Fasting glucose mg/dL)/405

<1.0 means you are insulin-sensitive which is optimal.> 1.9 indicates early IR.> 2.9 indicates significant IR.**3.3 25-hydroxyvitamin D levels**Vit. D deficiency Criteria; Serum level1. 10-20 ng/mL deficient
2. > 10 ng/mL severe deficient
3. =/> 25 ng/mL normal

**3.4 Estimation of Circulating microRNAs*** miR-375
* miR-96
* miR-124a
* Insulin resistance receptors miRNA.

**Data collection;**In collaboration with Ministry of Health, data from Diabetes Centres in Erbil, Duhok, and Sulaimani will be collected. A homogenous cohort (male and female, 25-65 years) of Vitamin D deficient in prediabetics will be recruited for the randomized, placebo-controlled trial after obtaining informed consent from participants and approval of the Ethic Committee Board. |
| **6. Scope and limit to the research**This research involves Endocrinology in Human pathophysiology and biology which may uncover some problems such as; 1. Due to financial crisis, diabetes health centers may not be able to accommodate researchers.
2. Some of patients/cases may not easily convinced to cooperate and may refuse to give samples.
3. Some of patients/ participants may quit or cut off contact during or in the middle of the research.
4. It may somewhat difficult for the patients to take their prescribed vitamin D supplements punctually.
5. The cost of the researches and the necessary tools may have an impact on the duration of the research.
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|  **8. Duration and timeline**The research may take at least three years from July, 2022 to June, 2025.  |
| **9. Conclusions**This is a new and unique study in Iraq generally and in Kurdistan specifically means there isn’t any study on the affect and/or the role of vitamin D on prediabetic patients in Iraq till now, therefore we expect positive outcomes on the correlation between vitamin D deficiency and diabetics’ complications. |
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