Vitamin D status and its relation to glycaemic control in children and adolescents with type 1 diabetes mellitus

Thesis submitted for partial fulfillment of the MD degree in Paediatrics

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(وَعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيماً)

صدق الله العظيم

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Abstract

This prospective cohort study screened fifty children and adolescents with T1D for vitamin D deficiency. 70% were found to have vitamin D deficiency and were tested for the effect of vitamin D supplementation- for 3 months- on their glycaemic control. They had significantly higher insulin requirements compared to those with normal vitamin D levels. Vitamin D deficiency significantly correlated with insulin requirements and with HbA_1c%. Vitamin D supplementation improved HbA_1c% significantly but this improvement was not sustained 3 months later. However, no significant change in insulin requirements.

Keywords

HbA_1c%: (Glycated Hemoglobin).

T1D: (Type 1 Diabetes).

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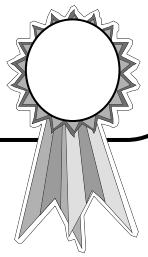
Dedication

I dedicate this work to all my family, whose love and prayers have helped me stay focused and achieve this great milestone. Words are not enough to express my gratitude to my mother for her endless help, everlasting support and her sustained encouragement.



List of Abbreviations

25OHD: 25 hydroxyvitamin D.

1,25 $(OH)_2$D: 1,25 di-hydroxyvitamin D.

CYP27B1: 1α hydroxylase enzyme.

ADA: American Diabetes Association.

BMI: Body mass index.

CSII: Continuous subcutaneous infusion insulin.

DKA: Diabetic Ketoacidosis.

GFR: Glomerular Filtration Rate.

HbA_1c: Glycated hemoglobin.

MDI: Multiple daily injections.

MODY: Maturity-onset Diabetes of the young.

SMBG: Self-monitoring of blood glucose.

T1D: Type 1 Diabetes.

T2D: Type 2 Diabetes.

Th1: T-helper cells type 1.

Th2: T-helper cells type 2.

UV: Ultraviolet.

VDBP: Vitamin D-Binding protein.

VDR: Vitamin D receptors.

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Introduction

Vitamin D is known to have anti-inflammatory and immunomodulatory effects. This could influence the autoimmune pathology of type 1 diabetes mellitus **(Hewison, 2010).**

There is evidence that vitamin D is important in the prevention of islet β cell death and improvement of insulin production, while low levels of vitamin D were shown to have a negative effect on β cell function **(Chiu et al., 2004).**

There is significant higher insulin requirement in type 1 diabetic patients with vitamin D deficiency together with low insulin sensitivity **(Tunc et al., 2011).** This is usually associated with higher fasting glucose and higher levels of glycosylated hemoglobin **(Kositsawat et al., 2010).**

Increasing vitamin D levels from 25 to 75 nmol/L was shown to improve insulin sensitivity by 60 % **(Schwalfenberg, 2008).**Vitamin D has been reported to raise insulin efficacy in type 2 diabetes mellitus, however, there is no studies, up till now, that define a similar relationship in type 1 diabetic patients **(Piccini et al., 2012).**

It has been postulated that vitamin D supplementation decreases insulin requirements together with improving metabolic control and pancreatic function in patients with type 1 diabetes **(El-Samahy et al., 2012).**

As there is insufficient evidence to show any beneficial effect of vitamin D supplementation on improving glycaemia or insulin resistance in type 1 diabetic patients **(George et al., 2012),** our study aims to investigate such correlation.

Aim Of Work

This study aims at screening for vitamin D deficiency in children and adolescents with type 1 diabetes and test the hypothesis that vitamin D supplementation would improve the glycaemic control and decrease the insulin requirements in such patients.

Chapter One

VITAMIN D

Vitamin D is popularly known as sunshine vitamin **Holick, (2007)**. There are two main sources of vitamin D for human beings: endogenous source through photosynthesis in the skin in response to sunlight exposure and exogenous source through dietary intake or supplementation **(Mathieu et al., 2005).**

Vitamin D can be obtained from dietary sources, but can also be sensitized. Ultraviolet B light induces cleavage of B-ring d of 7- dehydro-cholesterol in skin to yield the secosteroid vitamin D_3 **(Norman, 2008)**- [Figure (1)].

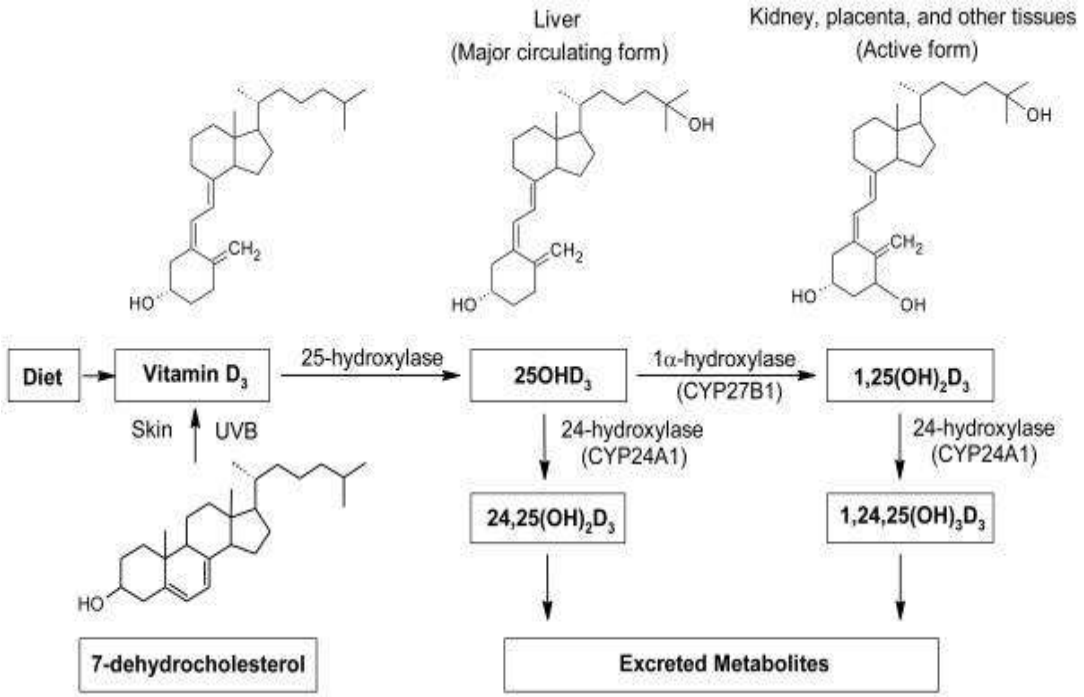

Figure (1): Synthesis of vitamin D **(Norman, 2008)**.

Vitamin D can be taken up via food, for example through fatty fish and their oils but most people achieve their vitamin D needs through UVB-mediated synthesis in the skin. Vitamin D concentrated in the blood depends on sun exposure and alimentary intake **(Holick, 2008; Yoshida and Stern, 2012).**

Tangpricha et al., (2003) found that only very few foods naturally contain vitamin D. Oily fish such as salmon (360 IV per 3.5 ounce serving), mackerel and sardines are good sources of vitamin D_3, as are irradiated mushrooms. Although egg yolks are reported to contain vitamin D, amounts are highly variable (usually no more than 50 IU per yolk) and the cholesterol content of egg yolks makes it a poor source of vitamin D. Cod liver oil which has been considered for more than three centuries to be critically important for bone health, is an excellent source of vitamin D_3. Very few foods are fortified with vitamin D, among fortified foods are milk and orange juice (100 IU per 8 ounce serving) and some breads and cereals- [Table (1)].

Table (1): Vitamin D Content of Foods **(Yeon-lee et al., 2013).**

Food	**Vitamin D Content,(international unit)**
Atlantic herring (raw)	1628/100 g
Butter	35/100 g
Canned pink salmon with bones in oil	624/100 g
Canned tuna/sardines/salmon/mackerel in oil	224–332/100 g
Cereal fortified	40/serving
Codfish (raw)	44/100 g
Cod liver oil	175/g; 1360/tablespoon
Cooked salmon/mackerel	345–360/100 g
Cow's milk	3–40/L
Dried shitake mushrooms (non-radiated)	1660/100 g
Egg yolk	20–25 per yolk
Fresh shitake mushrooms	100/100 g
Fortified milk/infant formulas*	400/L
Fortified orange juice/soy milk/rice milk	400/L
Margarine, fortified	60/tablespoon
Shrimp	152/100 g
Swiss cheese	44/100 g
Yogurt (normal, low fat, or non-fat)	89/100 g

*Infants consuming ≥ 1 L of formula daily do not require additional supplementation