Assessment of Vitamin D Status in a Group of Egyptian Children with Nocturnal Enuresis (NE)

Thesis

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

﴿فَأَمَّا ٱلزَّبَدُ فَيَذْهَبُ جُفَآءً ۖ وَأَمَّا مَا يَنفَعُ ٱلنَّاسَ فَيَمْكُثُ فِى ٱلْأَرْضِ ۚ كَذَٰلِكَ يَضْرِبُ ٱللَّهُ ٱلْأَمْثَالَ﴾

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Dedication

Words can never express my sincere thanks to ***My Family Specially my Parents*** *for their generous emotional support and continuous encouragement, which brought the best out of me. I owe them all every achievement throughout my life.*

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Abb.	Full term
25(OH)D	25-hydroxyvitamin D
ALP	Alkaline phosphatase
ANP	Atrial natriuretic peptide
APCs	Antigen-presenting cells
AVP	Arginine vasopressin
BVI	Bladder volume index
BVWI	Bladder volume wall thickness index
CaBP	Cytosolic calcium binding protein
CRE	cAMP response element
DCs	Dendritic cells
dDAVP	Desmopressin
ECG	Electrocardiograph
ELISA	Enzyme-linked immunoassay
FGF-23	Fibroblast growth factor 23
FHR	Familial hypophosphatemia rickets
GAGs	Glycosaminoglycans
HTN	Hypertension
ICCS	International Children's Continence Society
IL	Interleukin
IOM	Institute of Medicine
MRI	Magnetic resonance imaging
NE	Nocturnal enuresis
NKs	Natural killer cells
NMNE	Nonmonosymptomatic nocturnal enuresis
OSA	Obstructive sleep apnea

List of Abbreviations Cont...

Abb.	Full term
AAP	American academy of pediatric
ADH	antidiuretic hormone
AEDs	anti-epileptic drugs
OPG	Osteoprotegerin
PMCA1	Plasma membrane calcium ATPase
PMNE	Primary monosymptomatic nocturnal enuresis
PNE	Primary nocturnal enuresis
PTH	Parathormone
PTH	Parathyroid hormone
RA	Rheumatic arthritis
RANK	Receptor activator of NF-κB
RANKL	Receptor activator of NF-κB ligand
RDA	Recommended Dietary Allowance
RXR	Retinoic acid X receptor
SDB	Sleep-disordered breathing
SNE	Secondary nocturnal enuresis
UI	Urinary incontinence
UTI	Urinary Tract Infection
UVB	Ultraviolet B
VDD	Vitamin D deficiency
VDDR	Vitamin D deficiency rickets
VDI	Vitamin D intoxication
VDR	Vitamin D receptor
VDRE	Vitamin D response elements
Vit. D	Vitamin D

INTRODUCTION

Nocturnal enuresis (NE) is defined in accordance with the International Children's Continence Society (ICCS) as "intermittent nocturnal incontinence." Primary monosymptomatic nocturnal enuresis (PMNE) is defined as lifelong continuous "enuresis without any other history of lower urinary tract symptoms and without a history of bladder dysfunction." For all other children who do not fit these criteria, the broad term nonmonosymptomatic nocturnal enuresis (NMNE) is used ***(Schultz-Lampel et al., 2011).*** Children with NMNE may have a variety of different reasons for their enuresis, which should not be thought of as homogenous in cause or treatment ***(Nascimento-Fagundes et al., 2016).*** Reasons can include urinary tract infections, diurnal enuresis, and known anatomical or neurologic bladder dysfunction. A subset of children with NE who previously have had a dry period for 6 months or longer are characterized treatment in a and success of treating these conditions vary greatly among the different categories as having secondary NE ***(Hyuga et al., 2017).***

Nocturnal enuresis is the intermittent involuntary loss of urine at night, in the absence of physical disease, at an age when a child could reasonably be expected to be dry (by consensus, at a developmental age of five years) ***(Neveus et al., 2006).*** Nocturnal enuresis has a significant negative impact on the child's psychosocial well-being ***(Von Gontard et al., 2011).***

Children with nocturnal enuresis usually do not have daytime bladder symptoms and are deemed to have monosymptomatic nocturnal enuresis ***(Neveus et al., 2006)*** between 10% to 28% of children who wet during sleep at night also have bladder problems during the day (including daytime wetting)**.** These children are said to have non-monosymptomatic nocturnal enuresis. A total of 6.6% of children have combined daytime urinary incontinence and nocturnal enuresis ***(Caldwell et al., 2016).*** Although daytime urinary incontinence is a significant problem it is usually considered separately to nocturnal enuresis, as the aetiologies underlying the two conditions are thought to be different ***(Nevéus et al., 2010).***

Physical causes such as structural abnormalities and functional disorders of the urinary tract, including overactive bladder syndrome or urinary tract infections, are more often found in children who also have daytime wetting. If daytime symptoms are present, investigations to identify physical (organic) causes such as urinary tract dysfunction, congenital malformation and neurogenic disorders are usually necessary, with treatment initially focused on addressing the daytime urinary symptoms ***(Alloussi et al., 2009).***

Vitamin D (VitD) is an essential nutrient with hormone-like activity that regulates calcium and bone metabolism throughout life. Adequate VitD is required among children for effective bone mineralization and normal growth. Reduced

intestinal calcium and phosphate absorption and increased bone resorption might happen when the levels of VitD are too low. Furthermore, VitD insufficiency not only influences the bone formation of children, but it is also related to many other diseases, including respiratory infection, nocturnal enuresis, diabetes, and asthma in children ***(Geng et al., 2016).***

The major role of vitamin D in the human body is commonly thought to be related to calcium metabolism and bone structure. However, scientific evidence clearly indicates that the biological importance of this vitamin greatly exceeds these aspects. The 25-hydroxyvitamin D [25(OH)D] is the main circulating metabolite of vitamin D, and is considered to be an indicator of vitamin D status in the human body ***(Norman, 2008).*** Low 25(OH)D is considered to play an important role in the development of cardiovascular diseases, metabolic syndrome, type 2 diabetes mellitus, inflammatory and immune abnormalities, and sleep disorders ***(Gominak and Stumpf, 2012; Van der Schueren et al., 2012).*** Low 25(OH)D was associated with an increased risk of NE in children aged five to seven years ***(Li et al., 2014).***

Low 25(OH)D is proposed to contribute to immune dysregulation including inducing a relative elevation of circulating IL-1, IL-2, IL-6, TNFα and NFκB, all of which can result in subjective sleepiness symptoms ***(Li et al., 2014).*** Therefore, it is mechanistically plausible that suboptimal concentrations of 25(OH)D may contribute to poor sleep

quality by directly modulating immune-regulating substances. Together, these studies confirm the hypothesis that Low 25(OH)D contributes to sleep disorders, which, in turn, lead to an increase in the risk of NE. However, this hypothesis is still under discussion and need to be confirmed by further studies Sleep disorders may play a role in development of NE. Based on this finding, we measured serum 25(OH)D concentrations, effective on sleep patterns, in enuretic children ***(McCarty et al., 2012).***

AIM OF THE WORK

The aim of this study is to investigate whether there is any relationship between 25 hydroxy Vitamin D and nocturnal enuresis in comparison to normal population.

Chapter 1

NOCTURNAL ENURESIS

Enuresis (synonymous with intermittent nocturnal incontinence) refers to discrete episodes of urinary incontinence during sleep in children ≥5 years of age.Enuresis can be divided into primary enuresis (PE) and secondary enuresis (SE). A child who has never been dry is considered to have PE; a child who has been continent for at least 6 months before the onset of the bedwetting is considered to have SE. The pathogenesis of PE is similar to that of SE ***(Neveus, 2017: Robson, 2009).***

Primary nocturnal enuresis (PNE) describes bedwetting in children who are at least five years of age, have never established urinary continence, and have urinated in their beds at least twice per week for at least 3 consecutive months ***(American Psychiatric Association, 2013).***

In PE, psychological problems are almost always the result of the condition and only rarely the cause. In SE, however, psychological problems are a possible cause, albeit not a common one. The comorbidity of behavioral problems is two to four times higher in children with enuresis ***(Dossche et al., 2016).***

The emotional impact of enuresis on a child and family can be considerable. Children with enuresis are commonly