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Wafaa Raji Alfatlawi

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ORIGINAL STUDY

Synergistic Endocytic Receptor Ligand Receptor Protein 2 in T2DM

Wafaa Raji Alfatlawi

Applied Chemistry Department, College of Applied Science, University of Technology-Iraq

ABSTRACT

Purpose: The glycoprotein molecule known as megalin is present on the proximal renal tubular epithelial cells. With an emphasis on megalin and cubilin levels in T2DM and IR patients, an area that obviously needs more research, this study attempts to give an outline of current knowledge of megalin function in relation to vitamin D and its metabolite (vitamin D receptor and vitamin D binding protein). Materials and Methods: This was a case control comparative study conducted at a endocrine and diabetes center in AL-Imamain Kadumain teaching hospital in Baghdad-Iraq. Study subjects were divided into three groups: 25 with T2DM with age range 42–45 years, 25 with IR with age range 45–47 years, and 28 as healthy controls with age range 42–44 years. The enzyme-linked immunosorbent assay technique used to estimate serum megalin, cubilin, vitamin D status, and insulin while lipid profile and fasting blood sugar measured by using colorimetric enzymatic method. Results: serum megalin and cubilin levels were higher in the diabetic and insulin resistance subjects compared to healthy control. No correlation was found between serum megalin and cubilin with the biochemical parameters measured in this study. Conclusion: we conclude that megalin and cubilin develop vitamin D deficiency. Lack of presence or malfunction of either receptor is linked to their action by binding and a reduction vitamin D, VDR, and VDBP. The distribution of lipids, vitamins, and other nutrients depends on this interaction. Tubular proteinuria and complications with vitamin metabolism can result from defects in either receptor because they interfere with the reabsorption of carrier proteins.

Keywords: Megalin, Cubilin, Vitamin D

1. Introduction

The ability to take up substances from the surrounding environment not only provides cells with vital nutrients, but also enables selection transport of substances from one compartment to another. Megalin and cubilin are two structurally different endocytic receptors that interact to serve such functions. With an emphasis on megalin and cubilin levels in T2DM and Insulin Resistance patients, an area that obviously needs more research, this study attempts to give an outline of current knowledge of megalin function in relation to vitamin D and its metabolite vitamin D receptor (VDR) and vitamin D binding protein (VDBP) [1]. Evidence has accumulated in recent years to indicate that these receptors have important functions in both normal physiology and pathology. There are few studies on the role of these two receptors in patients with type 2 diabetes. Our aim show that vitamin D, VDBP, and VDR reabsorbed The protein shares extensive is filtered through the glomerulus and reabsorbed in structural in the proximal tubules by megalin , this lead to decreased their levels in the serum of diabetic and insulin resistance patients [2] In particular, Megalin and Cubilin receptors are important for providing substrate for renal hydroxylation and activation of vitamin D. Low density lipoprotein Receptor Related Protein 2 (LRP2) was identified as the antigen of rat experimental membranous nephropathy (Heyman nephritis) and originally named gp330 and subsequently megalin [3] and later LRP2. LRP2/megalin is a multiligand

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E-mail address: Wafaa.R.Mohammed@uotechnology.edu.iq (W. R. Alfatlawi).

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binding receptor found in the plasma membrane of many absorptive epithelial cells. LRP2 is an approximately 600kDa (4665 amino acids) transmembrane glycoprotein with structural similarities to the low-density lipoprotein receptor (LDLR) [4] LRP2 has a NPXY motif that is the binding site for Dab2 to initiate clathrinid-mediated endocytosis LRP2 forms a homodimer that changes conformation in response to pH. At pH 7.5 (extracellular pH), LRP2 is considered active, with the leucine loops in an open conformation to allow ligands to bind. At acidic endosomal pHs, the leucine loops collapse to prevent ligands binding [5] As megalin travels between various cellular compartments, it experiences substantial structural reorganizations in response to pH variations and operates as a dimeric complex [6]. Megalin is therefore exposed to the extracellular environment's neutral pH (about 7.4) when it is found at the cell surface. Megalin takes on "open" shape at neutral pH, which permits interaction with a variety of ligands. The pH falls to about 5–6 after internalization into the early endosome, which causes conformational changes that encourage ligand release [7]. Megalin is recycled to the cell surface after release, where the neutral pH returns it to its initial shape and enables it to bind to ligands once more. Megalin can effectively manage a high amount of endocytic traffic by continuously mediating the reabsorption of filtered molecules through this cycle of pH-driven conformational changes. At the proximal tubule brush boundary membrane, megalin interacts with the receptor protein cubilin and is further co-expressed [8]. Megalin functions to mediate endocytosis of ligands leading to degradation in lysosomes or transcytosis. LRP2/megalin can also form complexes with CUBAM, the cubilin and amnionless complex. Those complexes are able to reabsorb several molecules and can be inhibited by sodium maleate. LRP2 and CUBAM are responsible for the uptake of most of the filtered proteins that escape the glomerular filtration barrier in the proximal tubule of the kidney. The endocytic capacity of the proximal tubule cells is dictated by the combined function of LRP2, CUBAM, and disable homolog 2 (Dab2) [9]. Cubam, is the term used to refer to a multi-ligand receptor located in the terminal ileum, specializing in absorption of vitamin B12. Cubam is essentially composed of amnionless (AMN), and cubilin, it is essential as a cell receptor recognizing the "vitamin B12-intrinsic factor" complex, whereas amnionless is more involved in the receptor mediated endocytosis of the complex [10]. Protein reuptake in a proximal tubular epithelial cell mediated by megalin and cubilin. A simplified example of endocytosis mediated by megalin and cubilin is shown in the figure. A receptor complex made up of single megalin, cubilin, and amnionless (AMN) units is used to show the suggested dimeric megalin and cubam complexes. The apical membrane of the proximal tubule cell contains the megalin/cubilin receptor complex, which extends into the proximal tubular lumen. Here, it catches filtered protein, which causes the membrane to invaginate and an endocytic vesicle to develop, which ultimately joins an endosome. Protein is released from the receptor complex as a result of the endosomal compartments' low pH. While the receptor complex is recycled back to the brush boundary membrane, proteins are delivered for lysosomal breakdown [11].

2. Materials and methods

2.1. Patients and methods

2.1.1. Study design

A case control study was conducted for this research; patients were enrolled in this study at endocrinology outpatient department/ Al-Imamain Al-Kadhimain Medical City Hospital in Baghdad during the period from December 2024 to April 2025. Participants divided into three groups 25 with T2DM with age range 42–45 years, 25 with IR with age range 45–47 years, and 28 as healthy controls with age range 42–44 years. Healthy individuals with a fasting blood sugar below 120 mg/dL without any symptoms of diabetes. All participants were assessed through various metrics, including blood glucose levels, HOMA-IR, BMI and biochemical parameters.

2.2. Patients

2.2.1. Inclusion criteria

Patients with T2DM with age range between and those with IR

2.2.2. Exclusion criteria

Patients with tract infection, those with systemic arterial hypertension, those on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to ensure that the results were not confounded by these conditions or medications.

2.3. Sample collection

Serum samples were obtained from the subjects in a fasting state. Height, weight, and body mass index were recorded for all the subjects. All serum samples were collected in separate Eppendorf tubes for quantitative estimation of biochemical parameters.

2.3.1. Methods

This was a case-control comparative study conducted at the endocrine and diabetes center in AL-Immamen Kadumeen teaching hospital in

Table 1. ANOVA test of studied groups.

	Mean ± SEM			95 % CI		
	HC No. = 28	IR No. = 25	T2DM No. = 25	Lower	Upper	p-value
Age	40.43 ± 2.004	46.72 ± 1.512	44.27 ± 1.924	42.13	45.53	**0.12**
BMI	23.11 ± 0.611	29.00 ± 0.952	30.46 ± 0.912	26.21	28.58	**0.001**
Cubilin, ng/mL	0.460 ± 0.044	2.908 ± 0.158	2.652 ± 0.144	1.669	2.243	**0.001**
Megalin, ng/mL	1.211 ± 0.115	3.056 ± 0.111	2.725 ± 0.136	2.0645	2.5226	**0.001**
Vitamin D, ng/mL	19.717 ± 1.607	28.184 ± 1.818	25.725 ± 1.312	22.397	26.35	**0.001**
DBP, ng/mL	0.536 ± 0.066	0.474 ± 0.043	0.456 ± 0.043	0.430	0.551	0.522
VDR, ng/mL	2.448 ± 0.284	1.793 ± 0.142	1.855 ± 0.146	1.800	2.296	0.052
Insulin	6.373 ± 0.652	5.106 ± 0.281	5.411 ± 0.407	5.088	6.223	0.16
FBS, mg/dL	89.36 ± 1.668	214.20 ± 11.351	195.69 ± 10.390	147.93	179.79	**0.001**
HOMA-IR	1.407 ± 0.143	2.736 ± 0.242	2.662 ± 0.267	1.954	2.527	**0.001**
Cholesterol, mg/dL	151.43 ± 7.165	224.40 ± 13.860	218.50 ± 11.646	182.00	211.19	**0.001**
TG, mg/dL	107.18 ± 7.401	180.12 ± 16.483	193.88 ± 14.759	141.52	176.07	**0.001**
HDL, mg/dL	46.93 ± 4.076	45.60 ± 2.252	42.81 ± 2.233	41.65	48.65	0.623
LDL, mg/dL	84.96 ± 5.783	147.36 ± 13.714	141.69 ± 10.700	110.03	136.73	**0.001**
VLDL, mg/dL	21.57 ± 1.625	36.08 ± 3.310	39.73 ± 2.636	28.73	35.55	**0.001**

Baghdad-Iraq. Study subjects were divided into three groups: diabetic subjects T2DM, Insulin Resistance, and healthy control. ELIZA used to estimated serum megalin, cubilin, vitamin D, VDR, VDBP, and insulin. Following clearance from the Institutional Human Ethics Committee, the study designed and carried out in compliance with the Helsinki Declaration. A variety of lipid profile values were gathered from the laboratory information system, including total cholesterol, triglycerides, HDL-c, and LDL-c. fasting plasma glucose was also obtained.

2.3.2. Statistical analysis

SPSS Version 24 was used for statistical analysis. For continuous variables, mean ± SD was computed, and for categorical variables, percentages. The mean values for continuous variables were compared using the student t-test. To determine the relationship between continuous variables, Pearson's correlation analysis was performed. To compare the mean values of more than two sets of continuous variables, a one-way analysis of variance (ANOVA) was performed. The threshold for statistical significance was set at $P < 0.05$.

3. Results and discussion

BMI in patient groups and control: results show a significance difference in BMI between studied groups; T2DM, IR, and HC with a p-value = 0.001 by using ANOVA test. Similar results found by many studies [11, 12]. A high BMI, obesity indication, is an important risk factor for T2DM and IR. Excessive body fat, particularly in the abdomen, leads to increased levels of fatty acids and inflammatory cytokines that disrupt insulin signaling, creating 1 insulin resistance. Weight losing and therefore a reduction in BMI, can improve insulin sensitivity and lead to better glycemic control in patients with T2DM. Body composition and various anthropometric markers have been used as indirect indicators of IR, such as waist circumference, BMI, total body fat, and visceral fat. Each of these metrics provides valuable information about the distribution and amount of fat in the body, aspects closely related to metabolic health [13]. Many studies indicate that natural killer cells play a crucial role in obesity-induced and inflammation, being activated in epididymal white adipose tissue. There, they enhance the recruitment of macrophages, exacerbating inflammation and being corelated with a higher risk of IR [14, 15].

Cubilin and Megalin in patient groups and control: In this study the mean serum cubilin and megalin levels showed statistically significant increased between cases and controls p-value = 0.001. In T2DM, cubilin and megalin receptor expression and function are altered, potentially contributing to many diseases that related to kidney function and bone turnover, this could affect and impair protein reabsorption, causing increase megalin levels and this will increase the excretion of an important biomarker. Elevated megalin are associated with rapid progression of T2DM. In the proximal renal tubule, megalin is a crucial endocytic receptor. Similar study found by Pedersen et al. [16], they revealed that megalin and cubilin increased in patients with T2DM and this effect on the recovery of normal and nephrotic levels of filtered albumin.

Vitamin D shows a statistical difference among the studied groups (p-value = 0.001), but the difference differs in a non-significant manner in VDR and DBP (p-value = 0.001). Baseline biochemistry laboratory parameters of study participants are shown in Table 1. The mechanism that the two endocytic

receptors, megalin and cubilin, play a crucial role in the reabsorption of the vitamin D status (VDBP and VDR). An essential receptor for this mechanism is megalin as T2DM seems to stimulate alterations in megalin expression, vitamin D-mediated regulation of megalin becomes relevant, given the relation between T2DM and renal megalin expression, this would ensure a conservation of systemic vitamin D levels through megalin-mediated endocytosis [17]. Renal conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ occurs initially within mitochondria of proximal tubule epithelial cells (PTECs). Megalin is abundantly expressed in the apical membranes of endocytic vessels, PTECs, microvilli, glomerular podocytes, dense apical tubules, and within lysosomes to a lesser extent. For PTECs to sense and respond to systemic differences and demands for $1,25(OH)_2D_3$ synthesis, the precursor $25(OH)D_3$ must gain intracellular access. The first theory, that free hormone hypothesis, states that the biological activity of vitamin D metabolites, including both $25(OH)D_3$ and $1,25(OH)_2D_3$, are intermediates by their unbound (DBP-free) forms in the circulation, which enter target cells through passive diffusion and not via an active transporting mechanism [14]. Support for the free hormone hypothesis comes from a DBP knockout mouse model in which calcium homeostasis was not significantly changed despite there being severe circulating $1,25(OH)_2D_3$ decrease [18]. However, CYP24A1 and CYP27B1 activities were significantly downregulated and upregulated, respectively, in the renal DBP-null mice, suggesting a compensatory pathway for the lack of DBP to maintain $1,25(OH)_2D_3$ levels [11]. This may, partially, clarify that the decrease of vitamin D and its metabolites in which lead to promotes hypocalcemia, stimulating high PTH production and, in turn, increased bone turnover [19]. Megalin was known as an endocytic receptor implicated in the tubular uptake of proteins. Many ligands have been identified: Vitamin-binding proteins (Vitamin D binding Protein), Apolipoproteins (HDL), Low-molecular-weight peptides and hormones (Insulin), enzymes and enzyme inhibitors. Although not all the ligands can be expected to be found in the glomerular filtrate, many are recognized markers of defective tubular reabsorption. In our study some of ligands appear in low levels, this could explain and suggest the mechanism that megalin and cubilin could affect by their endocytosis uptake and degradation, similar study done by [20]. Vitamin D deficiency is related with different medical conditions like: metabolic diseases, musculoskeletal disorders, cardiovascular disease, and infection [21]. In proximal tubule Megalin and cubilin, the endocytic receptors of vitamin D binding protein from the glomerular filtrates and the subsequent intracellular responsible of conversion of 25-hydroxyvitamin D3 to biologically active 1α,25-dihydroxyvitamin D3, these receptors dysfunction which is commonly found in patients with diabetic and IR, even at early stages, may explain why vitamin D deficiency is often noted and complicated in those patients [22]. To protect the functions of these receptors, therapeutic strategies could be used to prevent vitamin D deficiency and its related complications [23]. Our results showed that the correlation between parameters studied were weak and appear in non-significant differences, this suggests more sample size or classification of studied groups according to other variables. So far, no anti-megalin antibodies have been related with any human renal disease with T2DM [24]. However, circulating anti-megalin antibodies have been evaluated in serum from patients with T2DM as well as some other thyroid diseases. Whether these antibodies are involved in the pathogenesis of the underlying autoimmune disease remains to be established.

Table 2. Post hoc ANOVA (sheffe test).

Parameters	p-value between groups		
	IR vs HC	DM2 vs HC	IR vs DM2
Age	0.24	0.179	0.654
BMI	**<0.001**	**<0.001**	0.473
Cubilin, ng/mL	**<0.001**	**<0.001**	0.353
Megalin, ng/mL	**<0.001**	**<0.001**	0.171
Vitamin D,ng/mL	**0.001**	**0.030**	0.563
DBP, ng/mL	0.708	0.556	0.972
VDR, ng/mL	0.091	0.139	0.979
Insulin	0.191	0.374	0.910
FBS	**<0.001**	**<0.001**	**<0.001**
HOMA-IR	**<0.001**	**<0.001**	0.973
cholesterol, mg/dl	**<0.001**	**<0.001**	0.933
TG,mg/dl	**<0.001**	**<0.001**	0.768
HDL,mg/dl	0.954	0.632	0.819
LDL,mg/dl	**<0.001**	**<0.001**	0.929
VLDL, mg/dl	**<0.001**	**<0.001**	0.613

FBS show significant difference between patients and control, while there was non-significant difference in Insulin p-value > 0.05. HOMA-IR results show statistically significant difference between patients' groups and control (p-value $= 0.001$). There was statistically significant difference in lipid profile in the study groups except HDL that show non-significant difference p-value > 0.05.

The sheffe post hoc test in the Table 2. Show that there was non-significant difference in age in studied groups. The comparison of cubilin, megalin, and BMI show significant difference when compare IR and T2DM with control. There was non-significant difference in DBP, VDR, and Insulin when comparing patients' groups with control. FBS show significant difference in all studied groups. Correlations between all parameters studied summarized in Table 3 that

Table 3. Correlation test.

Characteristic	Cubilin		Megalin	
	r	P	r	P
Cubilin,ng/mL	1			
Megalin,ng/mL	–0.032	0.823	1	
Vitamin D,ng/mL	0.248	0.079	–0.001	0.992
DBP, ng/mL	–0.106	0.461	0.112	0.434
Vitamin D Receptor, ng/mL	–0.184	0.202	0.014	0.922
Insulin	–0.112	0.435	0.119	0.405
Fasting Blood Sugar	–0.035-	0.809	–0.083	0.564
HOMA-IR	–0.107	0.457	0.067	0.638
Cholesterol, mg/dl	–0.188	0.187	0.156	0.276
TG,mg/dl	–0.124	0.386	0.002	0.989
HDL,mg/dl	–0.024	0.867	–0.093	0.517
LDL,mg/dl	–0.189	0.184	0.125	0.381
VLDL, mg/dl	–0.222	0.118	0.131	0.358
Age	0.185	0.193	0.148	0.299
BMI	0.047	0.745	–0.169	0.235

show weak and non-significant correlations between parameters.

4. Conclusions

Endocytic receptors that are highly expressed in the kidney's proximal tubule endocytic machinery are megalin and cubilin, they develop vitamin D deficiency. Lack of presence or malfunction of either receptor is linked to their action by binding and a reduction serum level of vitamin D, VDR, and VDBP. Despite having extremely distinct structures, the two receptors megalin and cubilin might work together. The megalin-cubilin interaction appears to be crucial for the endocytosis and recycling of the "peripherally attached" cubilin, and certain ligands are shared by both receptors. The metabolism of several hormones and vitamin-binding protein complexes, including the renal stimulation caused by the hydroxylation of vitamin D, depends on megalin. In T2DM, megalin and cubilin function is weakened, leading to decreased reabsorption of essential filtered substances like vitamins, proteins, and contributing to diabetic kidney disease and potential deficiency of Vitamin D. Downregulation of these receptors in T2DM, affecting renal function and highlighting the need for further research into an important role as potential biomarkers for T2DM and as targets for therapeutic interventions.

Conflict of interest

None.

Ethical clearance

The University of Technology-Iraq's College of Applied Science's Applied Chemistry Department approved the study's protocol and ethical guidelines. Every participant in the study gave their informed consent in accordance with the Helsinki Declaration.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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None.

Author contribution

The author W.R. conceived of the presented idea and developed the theory and performed the computations, verified the analytical methods, discussed the results and contributed to the final manuscript.

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