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Impact of Maternal Protein Restriction on Wnt4 Expression and Histological Liver and Kidney Development in Rat Embryos

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Abstract:

Maternal protein restriction can negatively affect fetal growth and organ development, particularly in the liver and kidney, through structural and molecular alterations. This study aimed to investigate the effect of maternal protein restriction on Wnt4 gene expression and fetal liver and kidney development in rat embryos. The study included 30 adult female rats divided into a control group fed a 20% protein diet and two experimental groups (LP1 and LP2) fed low-protein diets (10% and 5%, respectively). Protein restriction was initiated two weeks before mating and continued throughout gestation. On day 20 of pregnancy, embryos were collected. Liver and kidney tissues were processed for histopathological examination using H&E staining, and Wnt4 gene expression was analyzed using real-time RT-PCR. Histological findings showed that both LP1 and LP2 embryos initially developed hematopoietic elements, followed by a progressive reduction in these elements and the presence of abnormal erythrocytes. Liver sections from LP2 embryos showed inflammatory cell infiltration. Kidney development was delayed in LP1 embryos, while LP2 embryos exhibited severe tubular degeneration and marked suppression of nephrogenesis. Molecular analysis revealed that Wnt4 expression was highest in the control group and progressively decreased in LP1 and LP2 groups, with the lowest levels observed under severe protein restriction. Maternal protein restriction impairs fetal liver and kidney development and significantly reduces Wnt4 gene expression in a dose-dependent manner.

Key words: Maternal protein restriction; Wnt4; Kidney; Liver; Rat embryos.

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Introduction

The developing fetus is especially vulnerable, and its growth and adaptation are highly regulated;d maternal nutrition during pregnancy plays a crucial role in this process. Developmental factors such as protein intake are key contributors to cellular proliferation, tissue differentiation, and gene expression regulation. The developing fetus is particularly vulnerable to maternal nutritional status during pregnancy. Adequate protein intake is essential for normal fetal growth and organ development through its role in cellular proliferation, tissue differentiation, and gene expression. Maternal protein restriction has been the subject of considerable research in experimental animal studies, particularly in the rat, and has been demonstrated to elicit dramatic effects on nutritionally programmed intrauterine growth, organ development, and the long-term regulation of physiology in the offspring [1; 2]. Initial data showed that maternal protein restriction impaired protein turnover in fetal tissues, implying that there was an imbalance between protein synthesis and degradation that is critical for normal growth and development [3]. This dysfunction is primarily due to decreased availability of key amino acids, as they are necessary substrates for fetal tissue development. In line with this, maternal protein restriction reduced fetal supply of amino acids, leading to reduced fetal growth and abnormal development [4]. Additionally, the timing of protein restriction during pregnancy indicates the developmental outcomes as well as their severity. Maternal protein restriction early or late in pregnancy differentially affects growth and hepatic expression of insulin-like growth factor I (IGF-I), a primary growth and metabolism regulator [5; 6]. The liver, due to its central role in metabolic pathways and nutrient processing, is one of the target organs that can be altered by maternal dietary protein restriction. Widespread histological and functional changes in the fetal liver have been described. Maternal diets low in protein have been shown to permanently alter the organization of hepatocytes in the fetal liver [7]. Maternal protein restriction also induces a long-term change in hepatic metabolism in the offspring, suggesting a sustained metabolic programming effect [8]. On a molecular level, protein restriction promotes alterations to hepatic unfolded protein response pathways, reflecting hepatic cellular stress and compromised protein folding capacity [9]. Being a metabolically active organ, kidney development is also very sensitive to maternal nutritional imbalance. During fetal life, the kidney develops through morphogenetic processes that require precise control of both gene expression and signaling pathways. Impaired renal development and function due to maternal protein restriction. It also suppresses the diastolic renin–angiotensin system in neonatal rats, potentially predisposing the offspring to experimental hypertension[10]. In addition, maternal protein restriction alters kidney expression of the angiotensin receptors and aquaporins that are important in determining fluid balance and renal physiology [11]. In support of this possibility, a recent publication has reported that protein deficiency in fetal kidney cells not only has serious effects on kidney development [12] but also that primary cilia length is shortened with deficiency. Maternal protein restriction has widespread effects on gene expression at the genome-wide level across multiple tissues. Omics-based studies have provided evidence of key molecular changes occurring in the kidney and other organs, stressing the systemic influence of protein deficiency on developmental pathways [13]. Furthermore, maternal protein restriction effects on gene expression in the fetal hypothalamus imply systemic adaptations

beyond peripheral organs [14]. It is also involved in leptin signaling and metabolic regulation of progeny, affirming the role of perinatal programming [15]. Although the effects of maternal protein restriction on organ development have been intensively studied, the role of protein deficiency on Wnt4 expression has not been thoroughly investigated. This connection is crucial for clarifying the molecular mechanisms behind impaired kidney development by maternal malnutrition. So, this study aimed to investigate the effect of maternal protein restriction on Wnt4 gene expression and to evaluate the histological changes in the liver and kidney development of rat embryos

Methods

Experimental Animals

A total of 30 adult female rats (Rattus norvegicus) were used in this study. The animals were obtained from the Animal House, College of Veterinary Medicine, Tikrit University, in September 2025. The rats were housed under standard laboratory conditions, including a controlled temperature (22 ± 2°C), a 12-hour light/dark cycle, and free access to food and water. All experimental procedures were conducted in accordance with institutional ethical guidelines for animal care and use.

Ethical Approval

All animal experimental procedures were reviewed and approved by the Research Ethics Committee, College of Education for Pure Sciences, University of Kirkuk, Kirkuk, Iraq. All experimental procedures were conducted in accordance with the institutional guidelines for the care and use of laboratory animals.

Experimental Design

The animals were randomly divided into three equal groups (n = 10 per group):

- Control group: Fed a standard diet containing 20% protein.
- Low Protein Group 1 (LP1): Fed a diet containing 10% protein.
- Low Protein Group 2 (LP2): Fed a diet containing 5% protein.

The dietary regimen was initiated two weeks prior to mating and continued throughout the gestation period.

Mating Procedure

After the adaptation period, females were housed with proven fertile males in a ratio of 2:1 (female: male) overnight. The presence of a vaginal plug the following morning was considered evidence of successful mating and was designated as gestational day 0 (GD0).

Sample Collection

Pregnant rats were sacrificed at gestational day 20 under appropriate anesthesia. The uterus was carefully dissected, and the embryos were collected. Liver and kidney tissues were excised from the embryos and divided into two parts:

- One part was fixed in 10% neutral buffered formalin for histological examination.
- The other part was immediately stored with Tri Zol for molecular analysis.

Histological Examination

The fixed tissue samples were processed using standard histological techniques. Briefly, tissues were dehydrated in graded ethanol, cleared in xylene, and embedded in paraffin. Sections of 5 µm thickness were prepared and stained with hematoxylin and eosin (H&E). The slides were examined under a light

microscope to assess structural and developmental changes in liver and kidney tissues [16;17].

Wnt4 Gene Expression Analysis

Total cellular RNA was isolated from embryonic kidney tissues using the SV Total RNA Isolation System (Promega, Madison, WI, USA) supplemented with RNase-free DNase I, according to the manufacturer's recommended protocol. The concentration and purity of the extracted RNA were determined using a spectrophotometer. One microgram of total RNA was reverse transcribed into complementary DNA (cDNA) using the QuantiTect Reverse Transcription Kit (Qiagen, Valencia, CA, USA), following the manufacturer's instructions. Quantification of Wnt4 mRNA expression levels was performed using real-time reverse transcription polymerase chain reaction (real-time RT-PCR). The reaction mixture contained SYBR Green fluorescent dye (DyNAmo SYBR Green qPCR kit; Finnzymes, Espoo, Finland). Amplification was carried out using a DNA Opticon system (MJ Research, Waltham, MA, USA). The PCR reaction protocol consisted of an initial denaturation at 95°C for 10 minutes, followed by 40 cycles of denaturation at 94°C for 10 seconds, annealing at 60°C for 15 seconds, and extension at 72°C for 15 seconds, with a final extension at 72°C for 5 minutes. Gene expression levels were normalized against the housekeeping gene GAPDH (Table 1). All reactions were performed in triplicate, and relative gene expression was calculated using the 2^-ΔΔCt method.

Table 1. Primer sequences used for real-time RT-PCR

Gene	Forward (5'–3')	Reverse (5'–3')	Product size (bp)	Ref.
Wnt4	CTGGAGAAGTGTGGCTGTGA	GGACTGTGAGAAGGCTACGC	108	18
GAPDH	ATGACTCTACCCACGGCAAG	TACTCAGCACCAGCATCACC	136	

Statistical Analysis

Data were analyzed using statistical software (e.g., SPSS). Results were expressed as mean ± standard deviation (SD). Differences between groups were assessed using one-way ANOVA followed by post hoc tests. A p-value of less than 0.05 was considered statistically significant (19).

Results and Discussion

No maternal mortality was recorded in any experimental group during the study period. However, clear differences in fetal development were observed among groups. Fetuses from protein-restricted groups (LP1 and LP2) showed reduced size and weight compared with the control group, with more pronounced changes in the LP2 group.

Histological study

Histological analysis performed on the liver sections of control groups indicated a well-maintained hepatic architecture (Figure 1), with a distinct central vein, regularly arranged hepatocytes, and well-defined hepatic sinusoids. Normally, the hepatic parenchyma was characterized by abundant hematopoietic elements, as well as anucleated erythrocytes, suggesting normal fetal hematopoietic activity. In the LP1 group, mild histopathological changes were noted. The sections of the liver contained a central vein with scattered megakaryocytes and hematopoietic elements. However, there was a significant decrease

observed in these parameters, along with hematopoietic elements and anucleated erythrocytes, compared with the control group, suggesting a moderate inhibitory effect of the treatment on fetal hepatic hematopoietic activity. More severe histological alterations were revealed in the LP2 group (Figure 3). There was a prominent decrease in hematopoietic activity, except in association with megakaryocytes and hematopoietic elements. This correlated with an additional reduction of both hematopoietic elements and anucleated erythrocytes compared with LP1 and controls. In addition, the lymphocyte infiltration was notable within the liver, indicating an inflammatory response associated with severe maternal protein restriction.

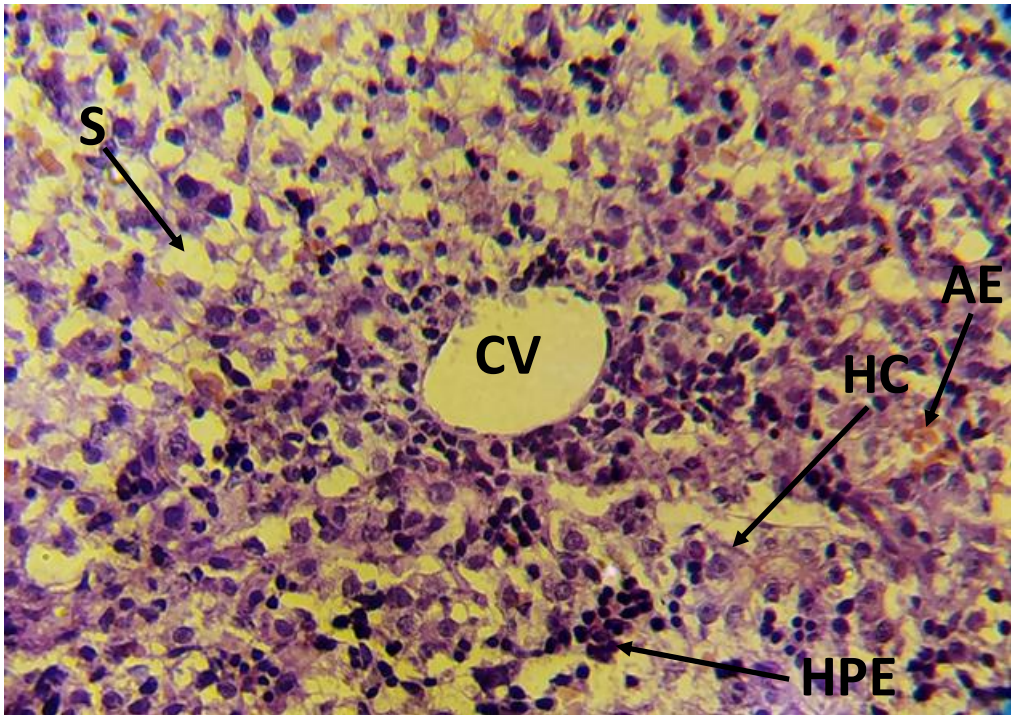

Figure (1): Liver of control embryo showing the normal structure of the Central Vein (CV), Hepatocytes (HC), and Sinusoids (S), with the presence of Hematopoietic Elements (HPE) and Anucleated Erythrocytes (AE). H&E, X400.

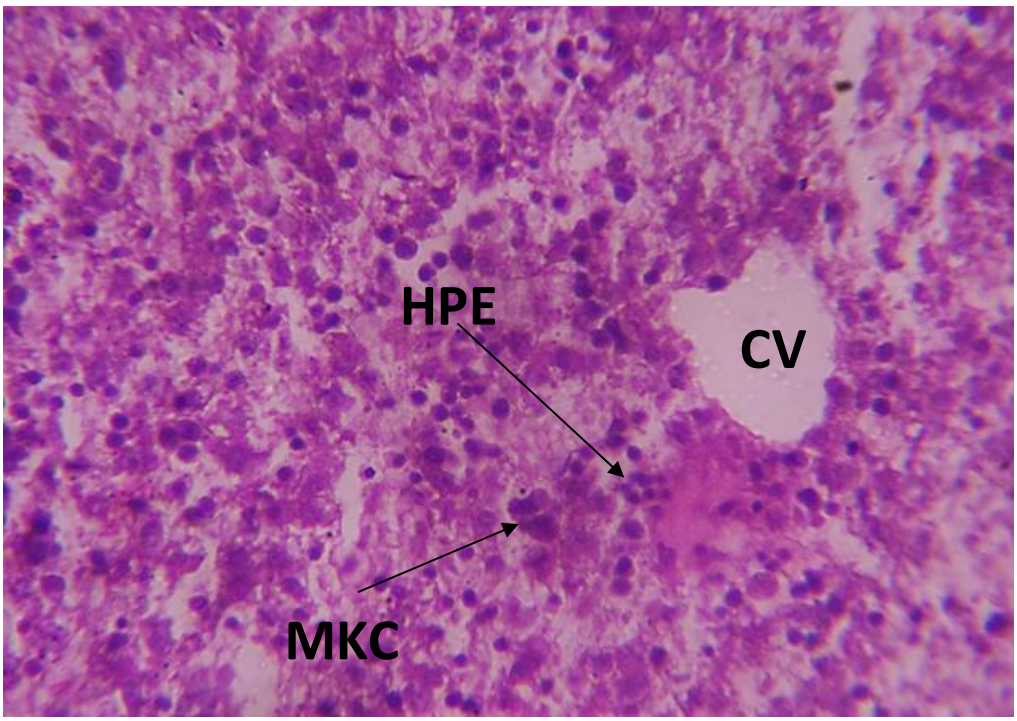

Figure (2): Liver of LP1 embryo showed Central Vein (CV), megakaryocytes (MKC), and Hematopoietic Elements (HPE) H&E, X400.

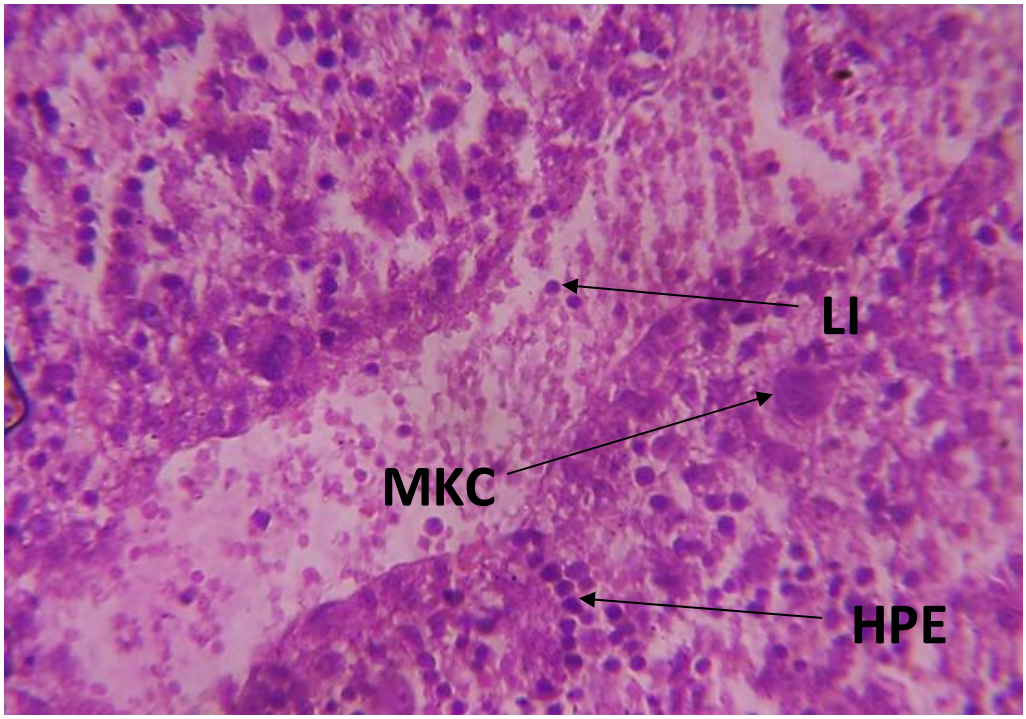

Figure (3): Liver of LP2 embryo showed megakaryocytes (MKC), and Hematopoietic Elements (HPE) with lymphocytes infiltration (LI). H&E, X400.

The diminished proportions of hematopoietic constituents and non-nucleated erythrocytes in the LP1 and LP2 groups indicate fetal hepatic hematopoiesis. These findings were consistent with the work of [4], who found that maternal protein restriction alters rates of protein turnover in fetal tissues, and that this effect on protein metabolism impairs the cellular growth of tissues and leads to reduced developmental efficiency. Similarly, a study by [5] determined that low-protein diets during pregnancy led to structural changes in fetal liver architecture and impaired hepatocyte organization, which correlates with the histological changes seen in this study. Hence, our findings would support the findings from this experiment in terms of the negative effect of protein restriction on fetal liver growth. In terms of the development of the kidneys, progressive structural damage was observed in the protein-restricted groups, especially LP2, with glomerular and tubular abnormalities. This is consistent with the finding by [6] showing that maternal protein restriction downregulates the renin–angiotensin system in progeny, which may be responsible for abnormal renal development and long-term hypertension. In addition, [18]documented that maternal protein restriction modifies renal expression of angiotensin receptors and aquaporins, providing the likely mechanisms for some of the structural and functional alterations observed in this study. Thus, these studies are consistent with our results regarding the sensitivity of kidney development to maternal nutritional status [19].

Histological examination of kidney sections from the control group (Figure 4) revealed normal renal architecture characterized by well-developed glomeruli (G) and normally arranged convoluted tubules (DT). In the LP1 group (Figure 5), mild histological alterations were observed. Kidney sections showed delayed growth and development of the glomeruli and renal tubules compared with the control group. In addition, damage in some convoluted tubules (DT) was detected,

indicating the adverse effect of maternal protein restriction on renal development. More severe histological changes were observed in the LP2 group (Figure 6). Kidney sections demonstrated marked retardation in the growth and development of both glomeruli and renal tubules. Furthermore, degeneration (D) of tubular epithelial cells was clearly evident in several renal tubules, reflecting severe renal tissue injury associated with pronounced maternal protein deficiency.

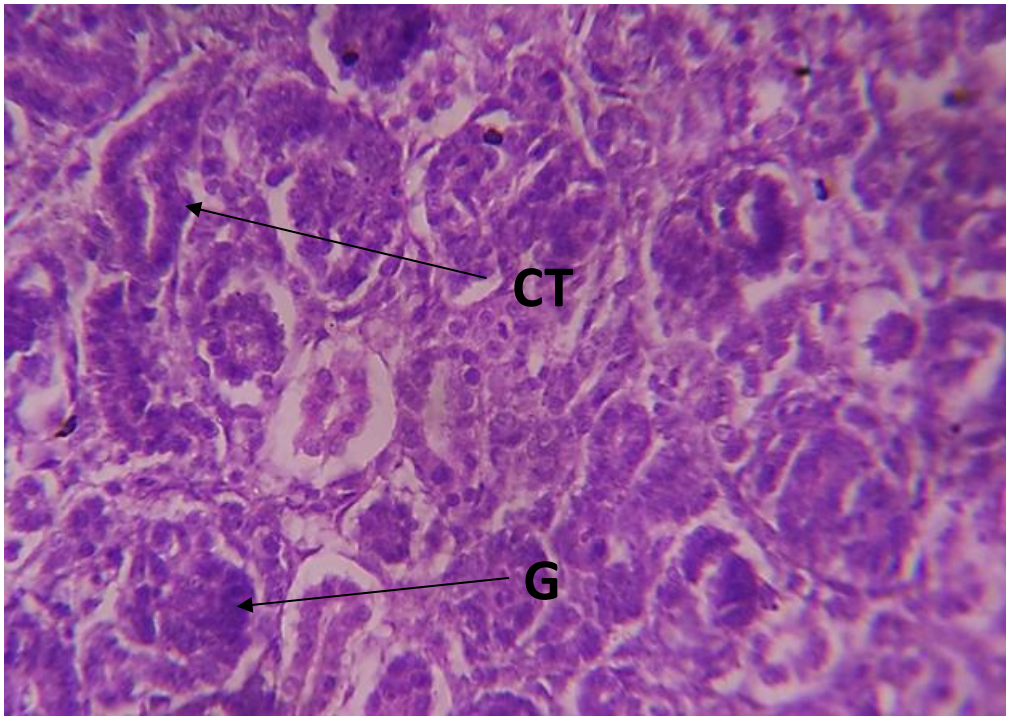

Figure (4): Kidney of control embryo showed normal glomerulus (G), and convoluted tubules (DT) H&E, X400.

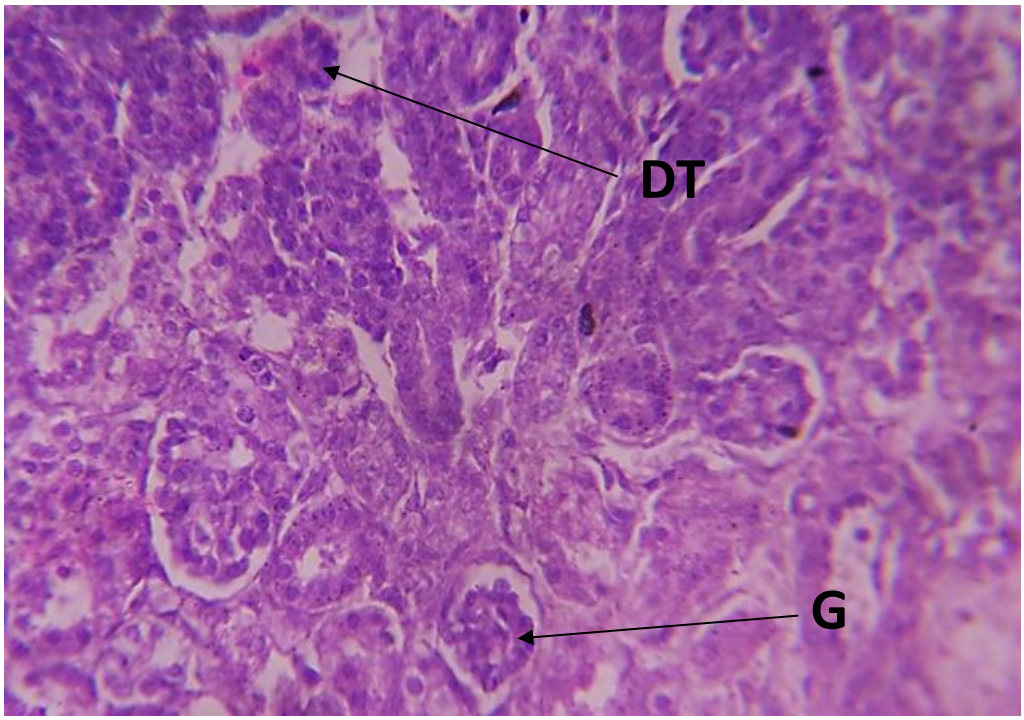

Figure (5): Kidney of LP1 embryo showed glomerulus (G), and damage of some tubules (DT) H&E, X400.

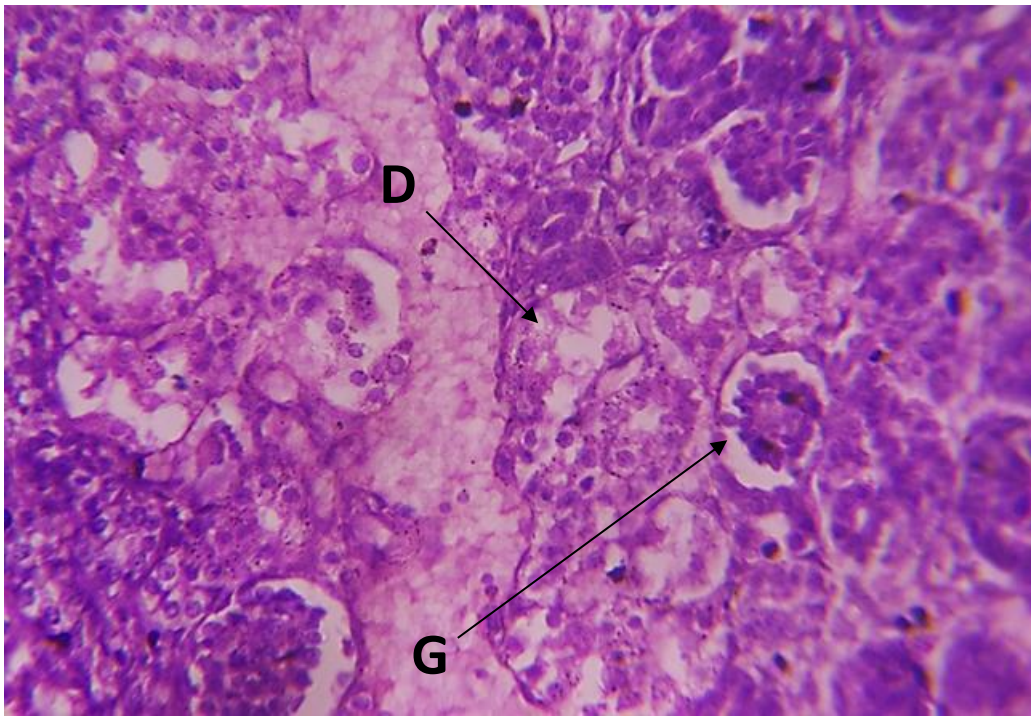

Figure (6): Kidney of LP2 embryo showed glomerulus (G), and degeneration (D) of cells in some tubules H&E, X400.

In agreement with [20], the present study demonstrates that maternal protein placental insufficiency causes crude malformations (microscopic and histochemical) of the kidneys of newborn rats, including poorly developed glomeruli and reduced tubular development in association with abnormalities in postnatal renal function. Changes in these characteristics are ascribed to impaired fetal growth due to protein depletion. Similarly, [21] showed that maternal protein restriction decreased nephron number and altered gene expression of perlecan, an extracellular matrix protein that plays a crucial role in nephrogenesis. These were also associated with cellular proliferation and apoptosis abnormalities in kidney development, which can explain renal maturation delay in this study. [22]Also provide evidence for severe tubular degeneration in LP2 embryos and suggest that maternal nutrient restriction primitively inhibits ureteric bud branching during nephrogenesis. Because ureteric branching is a requirement for nephron formation, hindrance of this process can result in reduced glomerular and tubular development. Alwasel et al. [23] reported that when pregnant dams are fed a protein-restricted diet, there is a decrease in fetal kidney angiotensin II receptor (AT1 and AT2) expression in the offspring. Due to the role of these receptors in nephron development and cellular proliferation, their decreased expression may contribute to the structural renal defects described in this study.

Wnt4 Gene Expression Analysis

The control group recorded the highest mean relative expression level (2^-ΔΔCt), with a value of 2.07. In contrast, the LP1 group showed a reduced mean expression level of 1.27, indicating moderate downregulation of Wnt4 expression. The LP2 group exhibited the lowest mean value of 0.64, reflecting marked suppression of Wnt4 gene expression (Table 2 & Figure 7). The reduction in Wnt4 expression was more pronounced in the LP2 group than in the LP1 group, indicating that severe maternal protein restriction had the greatest negative effect on Wnt4 gene expression.

Table 2. Expression levels of Wnt4 gene in kidney tissues of rat embryos exposed to maternal protein restriction.

Group	Wnt4	REFERENC	ΔCT	ΔΔCT	2-ΔΔCt	Folding	Mean
LP1	24.4	25.4	-1	0.375	0.771105413	0.771105413	1.271234
	22.7	25.3	-2.6	-1.225	2.337554497	2.337554497	
	24.1	25.6	-1.5	-0.125	1.090507733	1.090507733	
	24.1	25.3	-1.2	0.175	0.885767519	0.885767519	
LP2	24.9	25.6	-0.7	0.675	0.626332219	0.626332219	0.637106
	24.2	25.5	-1.3	0.075	0.949342121	0.949342121	
	25.6	25.4	0.2	1.575	0.335643126	0.335643126	
Control	22.1	25.6	-3.5	-2.125	4.362030931	4.362030931	2.071114
	24.1	24.5	-0.4	0.975	0.508739846	0.508739846	
	23.5	25.3	-1.8	-0.425	1.342572503	1.342572503	

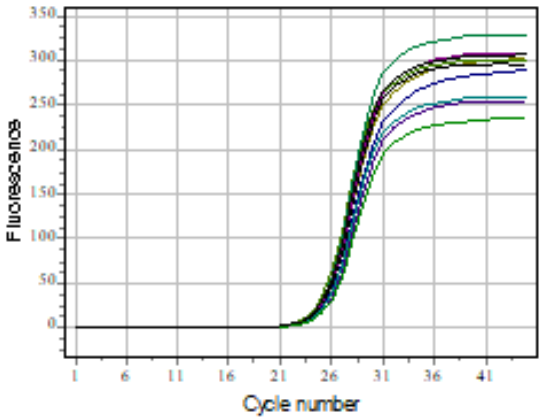

Figure 7. Expression levels of the Wnt4 gene in kidney tissues of rat embryos exposed to maternal protein restriction.

Among these signaling molecules, Wnt4 is one of the most important and best studied in terms of its role during kidney organogenesis, including at the stage when mesenchymal-to-epithelial transition begins to initiate nephron formation. [24] showed that Wnt4-/- mice do not develop functional nephrons because epithelial differentiation in embryonic kidneys is disrupted. Thus, the significant reduction of Wnt4 expression found in our study under LP2 exposure may account for severely impaired glomerular and tubular development as well as tubular epithelial cell deterioration. The histological data found in this study substantiate the molecular results. The LP1 group displayed delayed glomerular and renal tubule growth, while the LP2 group manifested pronounced tubular degeneration and marked

nephrogenesis impairment. These findings align with those of [10]found that maternal protein restriction inhibits the fetal renin–angiotensin system, with resultant disrupted renal development as well as nephron deficits in neonates. Similarly, [11] showed that a low-protein diet during pregnancy alters the renal expression of both angiotensin receptors and aquaporins, which are proteins essential for normal tubular differentiation /renal maturation. Similar explanations can be given for the observation of severe tubular degeneration in LP2 embryos, as nutritional deficiency may also affect both cellular proliferation and apoptosis. In this sense, [22] have demonstrated that restricted maternal nutrients inhibit ureteric bud branching in the developing kidney to limit nephron spaces, thus impairing renal structural development. Furthermore, [21] demonstrated that maternal protein restriction reduces expression of perlecan, an extracellular matrix component necessary for normal nephron development, and the resulting renal morphogenesis is abnormal. The striking downregulation of Wnt4 expression in the LP2 group indicates that maternal protein deficiency disrupts developmental signaling pathways at a transcriptional level. [25] support this interpretation that discovered Wnt4 signaling is required for nephron induction and tubular epithelial differentiation in the embryonic kidney. Alterations in Wnt signaling can also directly affect the histological defects seen here and may contribute to their correlation with Wnt4 disruption. In addition, recent studies using molecular techniques have demonstrated that maternal malnutrition results in permanent modifications of developmental gene expression and fetal programming. Maternal protein deficiency disturbs the primary cilia structure and affects renal developmental pathways in fetal rats [11]. As primary cilia are intimately associated with regulation of Wnt signaling, this may explain the diminished expression seen in both the functional assays and structural defects observed here for Wnt4 during kidney development. The cumulative data now also support the theory that maternal protein restriction produces developmental impairment in a severity-dependent manner. Maternal protein deprivation in the LP2 group resulted in the most significant suppression of Wnt4 expression and displayed a dose-dependent effect on fetal kidney development associated with intense histopathological changes compared with other groups

Conclusion

Maternal protein restriction produced striking histological changes in fetal liver and kidney tissues but suppressed Wnt4 gene expression considerably in whole rat embryos. Structural and molecular abnormalities were more pronounced in the LP2 group than in the other groups, with increasing severity exhibited as protein deficiency increased.

Conflict of Interest: Authors declare there is no conflict of interest.

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تأثير تقييد البروتين الأمومي على تعبير 4Wnt والتطور النسيجي للكبد والكلى في أجنة الجرذان

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المستخلص

يمكن أن يؤثر تقييد البروتين لدى الأم سلبًا في نمو الجنين وتطور أعضائه، ولا سيما الكبد والكلى، من خلال إحداث تغيرات بنيوية وجزيئية. هدفت هذه الدراسة إلى تقصي تأثير تقييد البروتين الأمومي على تعبير جين 4Wnt وتطور الكبد والكلى في أجنة الجرذان. شملت الدراسة 30 أنثى جرذ بالغة قُسمت إلى مجموعة سيطرة تغذت على حمية تحتوي على 20% بروتين، ومجموعتين تجريبيتين (LP) و(2LP) تغذتا على حميات منخفضة البروتين بنسبة 10% و5% على التوالي. بدأ تقييد البروتين قبل التزاوج بأسبوعين واستمر طوال فترة الحمل. وفي اليوم العشرين من الحمل، جُمعت الأجنة. تمت معالجة أنسجة الكبد والكلى للفحص النسيجي المرضي باستخدام صبغة الهيماتوكسيلين والإيوسين (H&E)، كما جرى تحليل تعبير جين 4Wnt باستخدام تقنية تفاعل البوليميراز المتسلسل بالنسخ العكسي الآني (Real-Time RT-PCR). أظهرت النتائج النسيجية أن أجنة مجموعتي 1LP و2LP شهدت في البداية تطورًا للعناصر المكوّنة للدم، تلاه انخفاض تدريجي في هذه العناصر مع ظهور كريات دم حمراء غير طبيعية. كما أظهرت مقاطع الكبد في أجنة مجموعة 2LP ارتشاحًا للخلايا الالتهابية. وقد لوحظ تأخر في تطور الكلية لدى أجنة 1LP، في حين أظهرت أجنة 2LP تنكسًا شديدًا في النبيبات الكلوية وتثبيطًا واضحًا لعملية تكوين النيفرونات (nephrogenesis).
أما التحليل الجزيئي، فقد بيّن أن تعبير 4Wnt كان الأعلى في مجموعة السيطرة، وانخفض تدريجيًا في مجموعتي 1LP و2LP، مع تسجيل أدنى مستويات التعبير في حالة التقييد البروتيني الشديد. تستنتج الدراسة أن تقييد البروتين الأمومي يعيق تطور الكبد والكلى الجنيني ويؤدي إلى انخفاض ملحوظ في تعبير جين 4Wnt بصورة تعتمد على شدة نقص البروتين.

الكلمات المفتاحية: تقييد البروتين الأمومي؛ 4Wnt؛ الكلية؛ الكبد؛ أجنة الجرذان.