6. Summary and Conclusion

Type 2 diabetes mellitus (T2DM) is a metabolic disorder of fuel homeostasis characterized by hyperglycemia and altered lipid metabolism caused by islet β cells being unable to secrete adequate insulin and insulin resistance. The elevated prevalence of this disease results in part from an increased rate of obesity in individuals with genetic predisposition for T2DM. Genetic studies have demonstrated that known variants account for less than 10% of the estimated overall genetic contribution to T2DM predisposition, suggesting that additional unidentified factors contribute to susceptibility of this disease. An important hypothesis for burdening of diabetes is called "developmental programming" or "fetal programming of diabetes". This concept assumes that, the maternal health challenges like malnutrition during gestation evoke a persistent physiological response in the offspring that may programs those offspring for the development of diseases like diabetes.

The present work was aimed to study the effect of pre-gestational maternal protein malnutrition on the expression of Uncoupling Protein 2 (UCP2) and mitochondrial transcription factor-A (mtTFA) as modulators in the glucose sensing of the different organs (pancreas, liver, muscles and adipose tissues) of the first generation rat offspring.

In this study 50 local female Wistar rats (one month age) were divided into two experimental groups:

- Group I: Control group (C) consisting of 25 rats feed normal control diet (20% protein) for 3 months
- Group II: Low–protein group (LP) consisting of 25 rats feed an isocaloric low-protein diet (LP; 8% protein) for 3 months

Following mating with normal male rats, all pregnant female rats (control and Low–protein) were allowed to give birth naturally. The offspring were weaned to either control diet or high-caloric diet and followed up for 30 weeks. The following parameters were assayed; glucose, insulin, non-esterified fatty acids (NEFA) and lipid profile. The rats was dissected out to obtain pancreas, liver, muscle and adipose tissues for assessment of insulin receptor, phospho-insulin receptor (P-IR) and mtTFA and UCP2 gene expression

In the present study, maternal protein malnutrition appears to affect pregnancy outcome as it caused significant decrease in the number of pups per litter and pups weight.

Follow up of F1 offspring indicated that, the male and female offspring of LP mothers became over weight and post-natal feeding with HCD further increases weight gain. This indicated obesogenic behavior of the offspring. The offspring of malnourished mothers maintained under control diet showed normal glucose tolerance and insulin sensitivity while those maintained under high caloric diet showed age- dependant decline in glucose tolerance and insulin sensitivity which became significant from the 15th week of age especially in male. With age 30 week, mild hyperglycemia was detected in the male offspring of LP mothers (under HCD only) while in females no hyperglycemia was detected and IGT was aggravated.

The histopathological data indicated that, the pancreas offspring of LP mothers under HCD showed sign of inflammation crowded and increased activity of β-cells compared to control. Immunohistological results revealed that the offspring of LP mother showed decreased total β-cell mass while the individual β-cell area and mass are significantly increased especially in the male rats under HCD.

The observed shifts in glucose homeostasis were associated with changes in the peripheral sensing of glucose in muscle, liver and adipose tissues assayed at the insulin receptor level as insulin receptor and it active fraction; phospho-IR.

The observed abnormalities in glucose homeostasis in the offspring of LP mothers are associated with lipid profile disturbances and elevated NEFA. Also, the gene expression of mitochondrial transcription factor A and uncoupling protein 2 the main player in

mitochondrial biogenesis and functions showed abnormal pattern in the offspring of LP mothers under HCD especially in the adipose tissues and liver .The expression of UCP2 appears to depend on the type of diets used especially in adipose tissues and liver.

From the results of the present study we con concluded that:

1- Pre-gestational and gestational low protein nutrition significantly decrease number of pups and pups weight
2- The offspring of protein malnourished mothers are at high risk for the development of T2DM as indicated by impaired glucose sensing, insulin resistance and hyperglycemia
3- Pre-gestational and gestational maternal protein malnutrition affects the offspring insulin sensitivity and glucose sensing parameters in the different peripheral tissues.
4- The post-natal diets differentially affect the studied parameters; as the control healthy balanced post-natal diets has no effect or even ameliorate the glucose sensing and insulin sensitivity in the offspring while high caloric post-natal feeding reverses the situation completely; as the offspring showed derangements in the glucose sensing (down regulation of insulin receptor and phospho-insulin receptor)
5- The offspring of LP mothers especially those feed HCD showed features of dyslipidemia and elevated non-esterfied fatty acids
6- The same offspring showed disturbed pattern of gene expression of mitochondrial transcription factor A and uncoupling protein 2 which control mitochondrial biogenesis and functions
7- The male offspring of LP mothers appears to be more susceptible for development of T2DM than female offspring.

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٨-الملخص العربى

داء السكري من النوع الثانى (T2DM) هو اضطراب التمثيل الغذائي لتوازن الطاقة ويتميز بارتفاع السكر في الدم وإضطراب التمثيل الغذائي للدهون وذلك ربما يكون بسبب فشل خلايا البنكرياس من نوع بتيا (β) فى إفراز الأنسولين الكافي وأيضا مقاومة الانسولين. يرجع إرتفاع نسبة الاصابة لهذا المرض نتيجة لزيادة في نسبة السمنة لدى الأفراد مع استعداد وراثي للنوع الثانى من السكرى T2DM. ظهرت نظرية هامة قد تساهم فى الإصابة بالسكري وهى "البرمجة التنموية" أو "البرمجة الجنينية لمرض السكري".

ويهدف هذا العمل إلى دراسة التعبير الجينى لعامل النسخ الميتوكونديري-أ و البروتينات الفاصلة ٢ باعتبارها وسائل لإستشعار الجلوكوز في الأعضاء المختلفة و ذلك فى الجيل الأول من نسل الجرذان التى تعرضت لسوء التغذية (نقص البروتين) أثناء الحمل والرضاعة .

تمت الدراسة علي ٥٠ من إناث الجرذان (عمر شهر) تم تقسيمها الى:
المجموعة الأولى: اشتملت علي ٢٥ من اناث الجرذان تم تغذيتها بطعام متوازن عادي (بروتين ٢٠٪) لمدة ٣ أشهر.
• المجموعة الثانية: مجموعة منخفض البروتين، اشتملت علي ٢٥ من اناث الجرذان التى تتغذى على نظام غذائي منخفض البروتين (بروتين ٨٪) لمدة ٣ أشهر.

بعد التزاوج و الولادة تم فطام النسل على إما نظام غذائى متوازن أو عالي السعرات الحرارية ومتابعتها لمدة ٣٠ أسبوع.
اظهرت نتائج ان سوء تغذية الأمهات بالبروتين اثناء الحمل و الرضاعة قد أثر على ناتج الحمل حيث انه تسبب فى انخفاضا ملحوظا في عدد الجراء و كذلك وزنها و ذلك بالمقارنة مع المجموعة الضابطة.
و بمتابعة الجيل الأول من النسل أشارت النتائج إلى زيادة وزن الجراء فى كل من الذكور والإناث من نسل الأمهات سيئة التغذية خاصة التى تم تغذيتها بعد الولادة بنظام غذائى عالى السعرات. وهذا دليل على إحتمالية حدوث سمنة فى هذه المجموعة.

أيضا أظهرت النتائج أن نسل الأمهات سيئة التغذية و التى تغذت على النظام الغذائي العادي بعد الفطام على تكون قادرة علي تحمل الجلوكوز وحساسية الانسولين بشكل طبيعى في حين أن النسل الذين تم وضعهم على نظام غذائي عالى السعرات الحرارية أظهرت انخفاضا ملحوظا في تحمل الجلوكوز والحساسية للانسولين مع التقدم بالسن والذى بدا واضحا من الأسبوع ١٥ من العمر خاصة في الذكور. مع التقدم في السن حتى الأسبوع ٣٠ تم اكتشاف زيادة متوسطة فى مستوى السكر بالدم في الذكور من الأمهات سيئة التغذية (تحت نظام غذائي عالى السعرات الحرارية فقط) بينما في الإناث لم يتم اكتشاف ارتفاع السكر في الدم مع تفاقم خلل تحمل الجلوكوز.

وأشارت نتائج الفحص المناعى لبنكرياس نسل الأمهات سيئة التغذية تحت نظام غذائي عالى السعرات الحرارية أظهر علامة على التهاب خلايا بيتا مقارنة مع المجموعة الضابطة.
ارتبطت التغيرات الملحوظة في توازن الجلوكوز مع التغيرات في عوامل استشعار الجلوكوز الطرفية في العضلات والكبد والأنسجة الدهنية وذلك عن طريق تعيين مستوى مستقبلات الأنسولين و مستقبلات الأنسولين النشطة (Phospho-IR).
صاحبت التغيرات التي لوحظت في توازن الجلوكوز في نسل الأمهات سيئة التغذية اضطرابات فى مستوى الدهون وإرتفاع فى الاحماض الدهنية (NEFA) بالدم. أيضا أظهر التعبير الجينى لعامل النسخ الميتوكونديري-أ و البروتينات الفاصلة ٢ و هما عاملان رئيسيان في تخليق و وظيفة الميتوكوندريا نمط غير طبيعي في نسل الأمهات سيئة التغذية تحت نظام غذائي عالى السعرات الحرارية خاصة في الأنسجة الدهنية والكبد مما يظهر إعتماد التعبير الجينى بهما على نوع الأنظمة الغذائية المستخدمة وخاصة في الأنسجة الدهنية والكبد.

من نتائج هذه الدراسة قد استنتجنا ما يلى:

١. سوء التغذية بالروتين فى مرحلة ما قبل الحمل والحمل يقلل بشكل ملحوظ عدد ووزن الجراء.

٢. نسل الأمهات سيئة التغذية بالبروتين هم عرضة لحدوث مرض السكرى من النوع الثانى كما دل على ذلك ضعف استشعار الجلوكوز ومقاومة الأنسولين وارتفاع السكر في الدم.

٣. سوء التغذية بالبروتين الأمهات ما قبل الحمل والحمل يؤثرعلى حساسية الأنسولين وعوامل استشعار الجلوكوز في الأنسجة الطرفية المختلفة فى نسلهن.

٤. النظام الغذائي بعد الولادة يؤثر بشكل متمايز على المعاملات التى تم دراستها حيث أن التغذية بالوجبات الغذائية الصحية المتوازنة بعد الولادة ليس له تأثير بل حَسّنَ من استشعار الجلوكوز وحساسية الأنسولين في هذه الذرية على عكس التغذية عالية السعرات بعد الولادة تماما حيث أظهر خللا في استشعار الجلوكوز (إنخفاض مستقبلات الانسولين ومستقبلات الانسولين الفوسفورية).

٥. نسل الأمهات سيئة التغذية بالبروتين خاصة التى تغذت على نظام غذائى عالى السعرات أظر زيادة فى الدهون بالدم و إرتفاع فى الأحماض الدهنية .

٦. أظهرت نفس الذرية إضطراب في التعبير الجيني لكل من عـــامل النســـخ الميتوكونديري-أ و البروتينات الفاصلة (٢) و التي تتحكم في البناء الحيوي للميتوكوندريا ووظائفها.

٧. الذكور من نسل الأمهات سيئة التغذية يبدو أنهم أكثر عرضة لتطور السكري من النوع الثاني من الإناث.

بسم الله الرحمن الرحيم

دراسة تأثير سوء التغذية فى الأمهات على التعبير الجينى لكل من جين البروتينات الفاصلة (٢) و جين عامل النسخ الميتوكوندورى (أ) في الانسجة المختلفة للجيل الاول من نسل الجرذان

رسالة
مقدمة إلى معهد البحوث الطبية
جامعة الإسكندرية
إيفاءاً جزئياً للحصول على
درجة الدكتوراة
فى
الكيمياء الحيوية
من

محمود صلاح محمد بدر

بكالوريوس علوم- كيمياء حيوية
كلية العلوم
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