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Dietary Proteins, Developmental Programming, and Potential Implication in Maternal Obesity

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ABSTRACT

Background: Proteins are known mainly based on their metabolic and nutritional functions including protein synthesis and a source of energy. In spite of various physiological properties attributed to proteins, their functions have neither been addressed by assessing quality of proteins nor by nutrition and dietetic practices. **Methods:** Studies were included if they were randomized animal studies, clinical trials and systematic reviews/meta-analysis published in English language. **Results**: The effect of maternal diet in general and dietary proteins in particular during development on health of offspring has been well-studied. Protein content as well as source of protein in the diet consumed during pregnancy and lactation influenced the risk of metabolic syndrome characteristics in offspring. Both high and low protein diets showed detrimental effects on health of offspring. Moreover, comparison of maternal casein-based diet with soy protein-based diet showed more favorable effect on body weight, body composition, blood pressure, and glucose metabolism in offspring. However, the role of maternal dietary proteins in developing the risk of metabolic syndrome characteristics in offspring in gestational obesity is still unclear and needs further study. **Conclusions:** Dietary proteins are determining factors in developmental programming. Both quantity and source of proteins in maternal diet influenced the development of metabolic syndrome characteristics in offspring. However, whether they have the same function in presence of gestational obesity is still unclear and needs further study.

Key words: *Dietary proteins; Developmental programming; Maternal obesity; Metabolic syndrome*

Introduction

The notion that fetal and early post-natal nutrition plays a major role in development of fetus and infant is not new and far from novel. There have been massive recommendations and prohibitions regarding maternal nutrition during pregnancy across the cultures for thousands of years. It is well-established that nutrition during pregnancy and lactation is a predominant factor in the development of somatic structures, endocrine

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systems, and homeostatic mechanisms in the fetus and infant. The novelty of this field origins from the fact that these effects influence the risk of chronic diseases including obesity, hypertension, diabetes, and cancer in later life (Adair *et al.*, 2001, Barker and Law, 1994, Eriksson and Olsson, 2004). The link between early ontogeny and later life health has been named fetal programming, which is defined as the process whereby a stimulus during a critical period of early development results in long-term physiological consequences (Kapoor *et al.*, 2006, Lucas, 2005). This critical window can be open even after birth and therefore, the developmental programming can be a more suitable term covering this crucial period. The developmental programming is the result of interaction between the in-utero and post-natal environments that has been captured in the Predictive Adaptive Response (PAR) hypothesis. According to the PAR hypothesis, offspring weaned to diets similar to those of their mothers will adapt more appropriately to their environment than those who receive an unmatched diet (Gluckman and Hanson, 2004). The role of maternal diet in general and dietary proteins in particular in developmental programming received considerable study. This review is an attempt to examine current findings in the field with more focus on maternal obesity and also to identify the gaps that need to be addressed in the future.

Materials and Methods

Studies were included if they were randomized animal studies, clinical trials and systematic reviews/meta-analyses published in the English language.

Results

Maternal obesity: Maternal obesity or gestational diabetes during pregnancy increases the risk of obesity and/or glucose intolerance in offspring (Fowden and Hill, 2001, Ogden *et al.*, 2014, Plagemann *et al.*, 1997). It is particularly important because more than two-thirds of women aged from 20 to 39 in the United States are overweight and/or obese and half of them are obese (de Campos *et al.*, 2007). An association has been found between increased nutrient supply before birth and later obesity. Intrauterine exposure to maternal obesity is associated with an increased risk of metabolic syndrome (Boney *et al.*, 2005) and obesity (Lawlor *et al.*, 2007) in later life. Obesity in mothers has been associated with gestational hypertension, preeclampsia, gestational diabetes (GDM), and high fetal birth weights greater than 4000 g. GDM results in hyperglycemia and hyperinsulinemia in the fetus during late development and higher risk of obesity in later life compared to infants of non-diabetic mothers (Boney *et al.*, 2005, de Campos *et al.*, 2007, Lawlor *et al.*, 2007, Ogden *et al.*, 2014, Plagemann *et al.*, 1997, Silverman *et al.*, 1991). Higher concentrations of insulin in fetus can potentially influence the development of regulatory systems permanently. For example, higher concentrations of plasma insulin within the immature hypothalamus may cause permanent alterations in life-long dysplasia of the central nervous nuclei regulating food intake and body weight (Dörner and Plagemann, 1994, Plagemann *et al.*, 1999). Fetal hyperinsulinemia can also lead to hyperhomocysteinemia (Fonseca *et al.*, 2002, Jiang *et al.*, 2007) that may results in DNA hypomethylation (Jiang *et al.*, 2007), causing further adverse effects on development of fetus (Jackson *et al.*, 2002, McMillen and Robinson, 2005). Obesity during pregnancy may also influence fetal growth and post-natal outcomes independent of GDM (Boney *et al.*, 2005, Lawlor *et al.*, 2007, Schäfer-Graf *et al.*, 1998, Silverman *et al.*, 1991). It has been suggested that in obese mothers without clinical signs of GDM, fetal hyperinsulinemia may occur due to maternal mild hyperglycemia which is below the threshold as defined for GDM.

Dietary proteins and developmental programming: protein content: Dietary proteins contribute to regulation of food intake, body weight, glucose and lipid metabolism, and blood pressure. Both amino acid composition (Jiang *et al.*, 2007, Lucas *et al.*, 1996, Ozanne *et al.*, 1996a, Ozanne *et al.*, 1996b, Petrie *et al.*, 2002,

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Rees *et al.*, 2000, Steegers-Theunissen and Steegers, 2003) and characteristics related to molecular structure of proteins including digestibility, bioactive peptides (BAPs) encrypted in their amino acid sequence (Anderson *et al.*, 2004, Daniel *et al.*, 1990, FitzGerald and Meisel, 2000, Froetschel, 1996, Jahan-Mihan *et al.*, 2011a, Lan-Pidhainy and Wolever, 2010, Leng *et al.*, 1985, Meisel, 1993, Nagata *et al.*, 2005, Nurminen *et al.*, 2000, Paroli, 1988, Pupovac and Anderson, 2002, Schusdziarra *et al.*, 1984, Teschemacher, 2003) and also their digestion kinetics (Boirie *et al.*, 1997, Fouillet *et al.*, 2002, Jahan-Mihan *et al.*, 2011a, Jahan-mihan *et al.*, 2011c, Leprohon and Anderson, 1982) are determining factors in their physiologic and metabolic properties. The effect of protein quantity in maternal diets during pregnancy on the risk of development of metabolic syndrome in offspring has been investigated. In rats, low protein maternal diets increase blood pressure (Rees *et al.*, 2000, sasaki *et al.*, 1982), body weight (Rees *et al.*, 2000), and adiposity (Leprohon and Anderson, 1982). However, high protein maternal diets increase body weight (Rees *et al.*, 2000), blood pressure, and food efficiency (Thone-Reineke *et al.*, 2006) but decrease energy expenditure (Beyer *et al.*, 2007, Daenzer *et al.*, 2002) in offspring. Nevertheless, low protein intake is less likely to be a major factor affecting majority of women's diets in developed countries. The average protein consumption in 20-39 years women in the US is 71.3 g/day (NAHNES 2011-12) which is far beyond the recommended amount of protein (46 g/day for women in the ages of 19-70+) (Nutrition for everyone, 2014). However, in spite of enormous studies on the role of maternal dietary proteins in fetal programming (Rush *et al.*, 1984), only a few studies have examined the role of a gestational high protein diet. In humans, a 40-g protein supplement added to the diets of black women during pregnancy resulted in lower birth weight in offspring compared to those born to mothers fed on a low protein supplement (6g as 7.5% energy) beverage (Rush *et al.*, 1984). The underlying mechanism is unclear at present. Moreover, postnatal high protein diet alone had no effect on body composition or metabolic rate (Beyer *et al.*, 2007). In rats, a maternal high protein diet fed throughout pregnancy and lactation resulted in higher blood pressure in male offspring compared with those born to normal protein fed dams (Langley and Jackson, 1994). In another study, maternal high protein diet resulted in higher body weight at the beginning of puberty, persisting until the end of the experiment (week 22), but just in female offspring of rats (Jahan-Mihan *et al.*, 2015). A high protein diet fed during gestation resulted in increased food efficiency (Petrie *et al.*, 2002) and lower energy expenditure (Beyer *et al.*, 2007, Daenzer *et al.*, 2002) However, the results from studies examining the effect of quantity of protein in maternal diet are not consistent. For example, “Hope Farm” and “South Hampton” low protein diets that have been used widely in various experiments in this field gave contradictory results: When the Southampton diet was given to the dams, higher systolic blood pressure was found in the offspring (Langley-Evans *et al.*, 1999, Langley and Jackson, 1994), the Hope Farm diet, resulted in normotensive, insulin-resistant offspring (Lucas *et al.*, 1996, Ozanne *et al.*, 1996a, Ozanne *et al.*, 1996b). It can be due to different protein sources that have been used in these diets.

Dietary proteins and developmental programming: Protein source: We previously reported that casein- and soy protein-based diets fed during pregnancy and lactation have different effects on the development of metabolic syndrome in rat dams and their offspring (Jahan-mihan et al., 2012). Fasting plasma glucose and insulin were higher in dams fed the soy protein diet compared with those fed a casein diet (Jahan-mihan et al., 2012) . At weaning, offspring born to the dams fed the soy diet had higher fasting plasma insulin, homeostatic model of assessment-insulin resistance (HOMA-IR) and homocysteine, and at week 15, higher body weight, body fat and HOMA-IR. Higher systolic (SBP) and diastolic blood pressure (DBP) were also found in the

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offspring born to the soy diet dams (Jahan-mihan et al., 2012). Offspring born to dams fed the soy diet had increased food intake compared with those born to the casein diet fed dams. In addition, higher insulin at weaning and 15 weeks post-weaning and higher hypothalamic mRNA expression of Agouti-related protein (AgRP) at weaning and higher plasma insulin, Glucagon-like peptide-1 (GLP-1) and ghrelin, in response to protein preloads characterized the offspring born to dams fed soy protein (Jahan-mihan et al., 2011b). Although weaning diet was also influential (Jahan-mihan et al., 2011c), maternal diet played a dominant role during the development and masked the effect of the weaning diet in majority of measured parameters in offspring (Jahan-mihan et al., 2011b, c, Jahan-mihan et al., 2012). Moreover, maternal diet influenced the phenotype of offspring in a sex-dependent manner. Female offspring were more resistant against changes induced by maternal diet compared with male offspring (Jahan-mihan et al., 2011d). Whether this observation is due to either the protective effect of sex-dependent hormones or due to the difference in development process in male and female offspring during pregnancy and lactation is still unclear and therefore an open window for further research.

It was also reported that structure and physicochemical properties of proteins fed during pregnancy and lactation are factors determining the effect of proteins on the development of metabolic syndrome in the offspring. In offspring born to dams fed on an amino acid-based diet (AAD), birth weight and body weight were lower while SBP and fasting blood glucose (FBG) were higher compared with those born to dams fed on an intact protein-based diet (IPD) (Jahan-mihan et al., 2017). The results of these experiments support the hypothesis that nutritionally complete diets differing in protein sources fed during gestation alone or during gestation and lactation have different effects on metabolic syndrome characteristics of offspring. Determining factors of such effects are structure and physicochemical properties of proteins. This study also showed that extending the duration of test diets from gestation alone to gestation and lactation resulted in a more robust effect of the diet on body weight, body composition, and glucose metabolism in offspring. This can be explained by the fact that the lactation period in rats is comparable with the third trimester of pregnancy in human (Jahan-Mihan et al., 2015).

Summary

The substantial role of consumed dietary proteins' quantity during pregnancy and lactation in developmental programming is well-established. Moreover, there are some evidences supporting the role of source as well as physicochemical properties of proteins in their effect on phenotype of offspring. Interestingly, nutritionally balanced maternal diets fed during pregnancy and lactation influenced development of various regulatory systems and eventually altered the phenotype of offspring differently when different sources of proteins were applied in these diets. It may support the notion that proteins, beyond their traditional role as the source of indispensable amino acids and energy, possess extensive physiologic and metabolic properties in a source-dependent manner. These functions of proteins cannot be simply explained by their amino acid composition. Various methods have been developed to evaluate quality of proteins including net protein utilization (NPU), biological value (BV), and more recently, the Protein Digestibility-Corrected Amino Acid Score (PDCAAS). However, their main focus is on determining the bioavailability of proteins and amino acids. Unfortunately, none of these methods can explain numerous physiologic and metabolic functions attributed to proteins. Moreover, the fact that dietary proteins can alter phenotype of offspring, even when they are given as part of a nutritionally complete diet, may suggest that the physiologic properties of proteins must be considered in nutrition recommendations when they are applicable. Lastly, in spite of abundant studies conducted in

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this field, the role of source and quantity of proteins in maternal diet in gestational obesity is still elusive. Whether a high protein diet plays a positive role in controlling appetite and calorie intake in obese mothers and consequently results in an improved pregnancy outcome or it deteriorates the development of the fetus and offspring, as it is reported in previous studies in normal weight mothers, is unclear currently and needs further investigation.

Conclusions

Dietary proteins are determining factors in developmental programming. Both quantity and source of proteins in maternal diet influenced the development of metabolic syndrome characteristics in offspring. However, whether they have the same function in presence of gestational obesity is still unclear and needs further study.

Conflicts of interest

The author declares no conflict of interest.

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