POHaD: why we should study future fathers

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Abstract

The growing field of 'Developmental Origin of Health and Disease' (DOHaD) generally reflects environmental influences from mother to child. The importance of maternal lifestyle, diet and other environmental exposures before and during gestation period is well recognized. However, few epidemiological designs explore potential influences from the paternal environment on offspring health. This is surprising given that numerous animal models have provided evidence that the paternal environment plays a role in a non-genetic inheritance of pre-conceptional exposures through the male germ line. Recent findings in humans suggest that the epigenome of sperm cells can indeed be affected by paternal exposures. Defects in epigenetic sperm mechanisms may result in persistent modifications, affecting male fertility or offspring health status.

We addressed this issue at the LATSIS Symposium 'Transgenerational Epigenetic Inheritance: Impact for Biology and Society', in Zürich, 28–30 August 2017, and here provide important arguments why environmental and lifestyle-related exposures in young men should be studied. The Paternal Origins of Health and Disease (POHaD) paradigm was introduced to stress the need for more research on the role of the father in the transmission of acquired environmental messages from his environment to his offspring. A better understanding of pre-conceptional origins of disease through the paternal exposure will be informative to the field of transgenerational epigenetics and will ultimately help instruct and guide public health policies in the future.

Key words: men; obesity; EDCs; sperm; DOHaD; epigenetic epidemiology

Introduction

Parents contribute in many ways to development and health of their children. A mother’s lifestyle is well recognized to have a positive or negative impact on her offspring’s health. However, the paternal contribution of early exposures is often overlooked in human studies. In recent years, a substantial number of animal studies have reported that fat-induced obesity, as well as several pre-conceptional environmental exposures (e.g. to certain food items, bisphenol A, heavy metals, stress, etc.), affect developing male germ cells. Acquired epimutations at this pre-conceptional stage of development may influence offspring’s future health [1]. Although not completely understood, comparative epigenetic mechanisms have been suggested in humans; discussed by others and us [2–7]. However, to date, empirical evidence on paternally transmitted effects in humans is still limited [8].

We here discuss two lifestyle exposures with a major public health burden: obesity and exposures to environmental pollutants, such as endocrine disruptors (EDCs) and other toxins from lifestyle habits, including smoking, alcohol intake and indoor pollution. Although excessive body fat is primarily due to a
combination of unhealthy dietary patterns and a sedentary lifestyle, exposure to a mix of as yet less well understood environmental factors, including endocrine-disrupting chemicals [9], may also affect metabolic homeostasis in the human body. These factors together contribute to what is currently termed the ‘obesogenic’ environment [10], which is omnipresent in a typical Western-lifestyle environment and part of the paternal exposome [8]. On the basis of animal data and a limited number of studies in humans, we recently introduced Paternal Origins of Health and Disease (or POHaD) as an extension of the DOHaD paradigm. We here explain why there is a need to study paternal influences on offspring and to inform young men who are planning to have a child. We provide a possible biological explanation and future research avenues. This will ultimately be beneficial to human health, especially in the context of the growing obesity burden and increasing environmental exposures to EDCs in the general population worldwide.

Why Focus on Obese Fathers-to-Be?

Obesity in Men

Adult overweight and obesity are major public health issues. Worldwide, reported prevalence has been increasing steadily in many populations [11] (http://www.who.int/mediacentre/factsheets/fs311/en/). While associations between obesity in women and offspring health are currently being extensively documented, paternal obesity is seldom included in epidemiological designs to investigate influences from parental lifestyles. Given the high frequency of obesity in adult men, this line of research should not be ignored. For instance, most recent national data of the US population show that overweight or obesity (BMI > 25) is 10% higher in men than in women (72.1% in men versus 61.2% in women) [11]. It is known that high BMI in men has deleterious effects on fertility parameters [12–14]. However, long-term effects, such as in subsequent generations, are unclear. We earlier showed a link between paternal obesity and offspring DNA methylation differences in humans [15, 16]. Furthermore, DNA methylation alterations in sperm have been associated with male obesity [17]. Yet, most evidence for an epigenetic link in the transmission of environmental conditions through the paternal germ line originates from animal data.

Obesity and Nutrition in Animal Models

A large number of experiments in animals showed that epigenetic marks can persist in a next generation, pre-disposing offspring with a different epigenetic pattern and altered phenotype which may often persist for many generations. In 2010, Ng et al. reported that high-fat diet consumption in male rats programmed β-cell dysfunction in F1 female offspring; combined with an early onset of impaired insulin secretion and glucose tolerance worsening over time [18]. DNA methylation changes were measured at a key pancreatic islet gene, I113ra2. Ng et al. added that the transcriptome of retroperitoneal white adipose tissue of offspring was also concomitantly affected [19]. However, no analyses were performed on sperm. Alhashem et al. demonstrated in a rat experiment that obesity, induced by a high-fat diet, has deleterious effects on semen. It diminishes total sperm count and the number of motile spermatozoa, while increasing morphological abnormalities. Parameters reflecting the oxidative status were also negatively impacted [20]. Other rodent studies showed that paternal obesity or malnutrition not only decreased sperm quality, it also affected early stages of development, with a decrease in embryo numbers and quality [21]. Aberrant offspring outcomes included an increased risk for impaired insulin sensitivity and adiposity [22]. Underlying molecular mechanisms in the male germ line are most likely the reason for these observations. Obesity or high-fat diet in rodents has been linked with changes in the sperm epigenome at multiple levels (microRNA and/or DNA methylation) [22–24]. De Castro Barbosa et al. showed that a diet-induced epigenetic response was paralleled by transgenerational inheritance of metabolic dysfunction throughout two generations [23]. Interestingly, also paternal vitamin levels may influence sperm and offspring health. If male rats were administered a folate deficient diet before mating, a decrease in global DNA methylation in the liver of the offspring was detected [25].

Physical Exercise Interventions in Animal Models

Further indications for the importance of a role of the sperm epigenome as an intermediate player between paternal health and offspring phenotypes originate from exercise intervention studies. McPherson et al. showed that an exercise-only intervention in obese male mice reduced the susceptibility to metabolic syndrome in offspring. The abundance of X-linked sperm microRNA was normalized after exercising [22]. Similarly, Palmer et al. showed that moderate exercising in obese mice reduced Reactive Oxygen Species (ROS) and DNA damage, and improved sperm motility and morphology [26]. Sperm quality and oxidative stress parameters were restored in rodents that were engaged in daily swimming, while simultaneously being fed a high-fat diet [20].

Some studies tried to quantify the effect of forced swimming on rodent sperm quality [27–29]. In brief, they found that forced exercising decreased normal morphology in spermatozoa [29], negatively affected spermatid production [27] and impaired fertilization capacity [28]. The forced exercising in these rodents is comparable to a high-intensity workout in humans.

Translating Animal Data on Physical Exercising to Humans

The animal models described above offer epidemiologists tools to help understand cellular processes in humans. At the same time, these animal data are useful to prevent that certain ‘Western’ lifestyle conditions—and resulting epigenetic marks in sperm—would be handed down to offspring. A remarkable observation from animal experiments is the improvement measured in sperm and offspring health after physical interventions. Furthermore, animal data show that extreme exercising or related stress prohibits the potential for amelioration. Hence, it is worth to explore if and how exercise intervention programs in humans influence sperm and offspring characteristics, including the epigenome.

In humans, along with dietary patterns, physical activity plays a major role in weight control [30]. Globally, 23% of adults are not active enough [11]. The Youth Fitness Survey as being part of NHANES in 2012 confirmed that obesity and physically inactive activity are closely interconnected. Moreover, this relation already starts in adolescence. Only 29.5% of normal-weight and overweight boys (aged 12–15 years old) met the daily recommended activity guidelines, meaning a moderate-to-vigorous activity for at least 60 min per day. Only 18% of the obese boys met this criterion [31]. Besides the negative health effects of obesity or a sedentary lifestyle, it is also well known that physical activity has positive effects on sperm quality in young men. However, the human body—and microenvironment of semen—responds differently according to the sport’s intensity (moderate versus...
effects from ‘their’ (human-induced) obesogenic environment. Domestic animals may also be beneficial in exploring epigenetic mechanisms generated from observational studies. Of note, studies on domestic animals may also be beneficial in exploring epigenetic mechanisms generated from observational studies. Of note, studies on domestic animals may also be beneficial in exploring epigenetic mechanisms generated from observational studies. Of note, studies on domestic animals may also be beneficial in exploring epigenetic mechanisms generated from observational studies. Of note, studies on
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that were not supposed to be paternally methylated were methylated if men were exposed to specific environmental chemicals. Interestingly, the more metabolites of these OP chemicals were measured in their urine, the higher the risk for producing a sperm sample that was hypermethylated at these imprinting regions. This suggests that a ‘cocktail’ of chemicals from the environment—which is realistic in our current daily environment—increases the risk of aberrant methylation in male germ cells. Interestingly, exposures to EDCs have also been shown to alter fatty acid composition and decrease anti-oxidant enzyme level in the testis [67], inducing oxidative stress [68] and ultimately affecting spermatogenesis [69]. Occupational exposures to bisphenol A was also shown to impact global sperm DNA methylation in humans [70].

Lifestyle habits such as smoking and alcohol intake can also be classified among environmental toxins. Chronic consumption of alcoholic beverages has been associated with sperm epigenetic aberrancies, such as DNA methylation at the IGF2 and H19 DM Rs [71]. Smoking habits have been correlated with changes in miRNA expression in spermatozoa [72]. Unfortunately, sample sizes were small in these studies. Noteworthy, the ‘Avon Longitudinal Study of Parents and Children’ (ALSPAC) provided evidence that sons of fathers who started smoking before puberty are at high risk of becoming obese [73]. Taken into account potential effects in children from smoking fathers it is worthwhile to proceed this line of research.

**Conclusions**

The environment of the father before conception not only predisposes him to obesity and related chronic disorders, but it can also affect his sperm quality, epigenetic profiles in spermatozoa, and increase the risk that his children will be obese or develop other chronic diseases [2].

At the LATSIS symposium we presented a number of epidemiological studies showing altered DNA methylation profiles in offspring at several differentially imprinting regions in children born from obese fathers [15, 16]. Some of these imprinted genes were also differentially methylated in sperm DNA of obese men (prospective fathers) [17]. Additional reports in healthy volunteers showed epigenetic aberrancies in sperm by increasing exposure to processed food and environmental toxins [74]. Although these findings in humans should be replicated in other populations, several experiments in animal models convincingly demonstrate that the sperm epigenome functions as a vector to transfer pre-conceptional environmental messages from paternal environment to offspring.

Obesity and exposures to EDCs are serious global health challenges. The increases in magnitude of obesity rates and exposures to environmental toxins have paralleled reports of rising frequencies of poor sperm quality, male infertility and several adverse health conditions. Next to these relatively immediate effects, the possibility that epigenetic marks can be transmitted to offspring opens a new field: that of POHaD [8]. An intermediate factor between obesity-related conditions and epigenetic signatures in sperm is oxidative stress. For instance, increased ROS can unbalance the epigenetic state. Hence, understanding interactions between the environment, ROS, and the epigenome in sperm is critical to acquire a comprehensive view on typical ‘Western’ diseases, today and in the future.

We believe that public health would doubly benefit from studies in men on protective effects from dietary supplementation and moderate exercising before conception. Besides advantages for the individual’s general and reproductive health, health of future offspring may also gain from this research. Health promotion and disease prevention is more challenging than curing diseases. However, without research in humans, we will continue to try and translate results from animal models to human beings, which may at best lead to speculation on the molecular processes in the human body.

As discussed by Rothstein et al. [75], evaluating the implications of personal lifestyles on epigenetics and offspring health becomes a social and ethical issue, even more so than research on the genetic origin of diseases. For instance, an unhealthy lifestyle could be used as evidence of lack of personal responsibility. The new and growing field of transgenerational epigenetics will thus generate the need for explicit attention to concerns about environmental justice in environmental regulations and health policies [75]. We here agree with the opinion of Rothstein et al. that additional scientific research (in humans) is needed before protective environmental policies can be implemented. Nevertheless, while our knowledge regarding the etiology of ‘transgenerational phenotypes or diseases’ is growing, it is advisable to inform and protect our most vulnerable populations, such as men with occupational exposures to EDCs, men with an unhealthy lifestyle, or those who are suffering from the consequences of subfertility.

In conclusion, understanding the mechanisms of action of EDCs or obesity-related exposures through germ cells will offer a unique opportunity to modulate risk for diseases in offspring via targeted recommendations of food supplements and a better lifestyle, or by introducing health policy recommendations requesting the industry to reduce or replace the use of certain chemicals. The current DOHaD concepts are already being used to guide public health policies that support mothers and children’s health. It has been well established that advising future mothers not to drink alcohol, not to smoke and to eat healthy, has important benefits for their offspring. Unfortunately, there is currently a striking lack of awareness in the general population regarding the father’s contribution to offspring health. We foresee a change in the historical concept of the mothers’ only contribution, to recognize and bolster the father’s role in success of having healthy children.

**Declaration of interest**

The author declares to have no competing financial, professional or personal interests.

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