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Abnormal Glucose Metabolism and Infertility

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Abstract

Background: Several studies have suggested that abnormal glucose metabolism, caused by the easy availability of calories and an increasingly sedentary lifestyle, is a cause of infertility. Indeed, specific foods have been shown to affect fertility by influencing related signaling pathways. Excess insulin has been shown to induce hormonal imbalances, which in turn can disrupt ovulation, egg quality, and conception, and women exhibiting insulin resistance often develop polycystic ovarian syndrome (PCOS). Similarly, a majority of diabetic individuals also suffer from infertility. Recently, our understanding of the relationship between glucose metabolism and fertility has greatly improved.

Methods: The published literature was systematically reviewed for case-controlled and cohort studies investigating infertility and glucose metabolism. A meta-analysis was then performed on all studies meeting well-defined selection criteria, as determined by two independent reviewers. The studies were critically evaluated using the Newcastle-Ottawa scale for non-randomized studies, before data were pooled and analyzed.

Main findings: Twenty-one articles were included in the final analysis, all of which provided the age, BMI, and ovulatory status of the subjects. A significant association between impaired glucose metabolism and infertility was observed. Additionally, impaired glucose metabolism was significantly more likely to occur where subjects were over 30 years of age, had a BMI of over 25 kg/m^2, or had metabolic syndrome. Impaired glucose metabolism was also associated with PCOS and infertility in women.

Conclusion: We have systematically pooled the available evidence, and we find a convincing causative link between altered glucose metabolism and serious fertility complications.

Keywords

Glucose metabolism; Infertility; Insulin; Glucagon; Amylin; GLP-1; GIP

Introduction

Mammalian systems have evolved to integrate environmental, nutritional, and hormonal signals in order to optimize reproduction. Such a system functions well in times of food shortage; however, the easy availability of food coupled with an increasingly sedentary lifestyle in recent times, and the impact this has on human metabolism, has had a profoundly negative effect on the reproductive system.

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Infertility is defined as the inability to conceive after one year of unprotected sexual intercourse, and reportedly affects 186 million people worldwide [1]. Body weight and constitution, physical activity levels, and nutrient consumption are all features that can impact fertility [2]. The misregulation of glucose metabolism, which is usually controlled by a delicate balance of the metabolic hormones insulin, glucagon, amylin, and incretin, was recognized as a cause of infertility several decades ago. Such alterations to metabolic activity are a consequence of the easy availability of calories, changing diets, and reduced energy expenditure due to lower levels of activity. Furthermore, specific foods have been shown to affect fertility by influencing particular signaling pathways [3,4].

In the year 2000, the protein insulin receptor substrate-2 (IRS-2), which transmits insulin signals during carbohydrate metabolism and is also important in female reproduction, was discovered. Studies of IRS-2 knockout mice showed that male mice developed non-insulin-dependent diabetes following IRS-2 loss, while female mice exhibited a reduction in mature follicles, which contain eggs during the reproductive cycle, as well as an absence of luteinizing hormone production, the hormone that triggers egg release [5]. IRS-2 has also been shown to synchronize reproduction and nurturing activities with internal carbohydrate homeostasis, which is vital for pregnancy and reproduction [6]. Insulin resistance is frequently reported in women with polycystic ovarian syndrome (PCOS), a disease commonly associated with hyperandrogenism and anovulatory-related infertility [7]. Furthermore, women with PCOS exhibited altered insulin receptor substrate-1 (IRS-1) activity, this being a protein that participates in glucose disposal and carbohydrate metabolism, leading to a significant decrease in insulin-facilitated phosphatidylinositol-3-kinase activity [8]. During times of low levels of circulatory glucose, glucagon, a hormone whose actions oppose those of insulin, is discharged into the blood. Similar to insulin, glucagon can also induce hormonal and ovarian responses. Conversely, incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), directly stimulate insulin production in order to lower blood glucose levels. Men who are overweight or obese exhibit numerous alterations in their body constitution and hormonal profiles, with notable changes in their levels of the hormones ghrelin, leptin, and GLP-1. Such hormones play a key role in the regulation of male reproduction, particularly spermatogenesis [9]. GLP-1 and GIP, which control the food-stimulated release of insulin from islet β cells in a glucose-dependent manner [10], reportedly influence testicular metabolism, and are important for glucose metabolism in Sertoli cells [11]. Furthermore, the gonads of male GLP-1-deficient mice were smaller, despite normal levels of sex steroids [12].

Glucagon secretions are inhibited by amylin, a gut-brain axis hormone that works in tandem with GLP-1 to boost insulin production. Amylin and insulin are released from the pancreas and are significant regulators of glucose metabolism [13]. Elevated levels of amylin and GLP-1 are associated with polycystic ovaries in women and erectile dysfunction in men [14].

Infertility can be distressing for patients, and presents challenges both for clinicians and for researchers who aim to understand its underlying causes and develop treatments. The estimated cost

of helping an infertile couple achieve a live birth is very high, and so furthering our understanding of infertility is of paramount importance. A great deal of work showing that fluctuations in glucose metabolism may contribute to infertility has been performed. Summarizing and interpreting the available evidence into the role of abnormal glucose metabolism in infertility will therefore empower healthcare professionals and policy makers to provide infertile couples with appropriate advice and treatment options. This meta-analysis attempts to comprehensively review the effect of unbalanced glucose metabolism on infertility in women, men, and animals.

Methods

Search strategy

The electronic databases PubMed, Enbase, Science Direct, Medline, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles published between January 2000 and December 2016. In addition, manual searches for relevant reviews and other systematic studies were performed. The search strategy involved the use of the following Medical Subject Headings (MeSH) as search terms: ['Glucose Metabolism' (MeSH) OR 'Abnormal Glucose Metabolism' (MeSH)] AND ['Infertility' (MeSH) OR 'Fertility Issues' (MeSH)] AND ['Pregnancy Outcome' (MeSH) OR 'Insulin' (MeSH) OR 'Glucagon' (MeSH) OR 'Amylin' (MeSH) OR 'Diabetes Mellitus, Type 2' (MeSH)] AND ['Polycystic Ovary Syndrome' (MeSH) OR 'Hyperandrogenism' (MeSH)].

Selection criteria

Studies reporting infertility amd abnormal glucose metabolism in men, women, or other mammals were included in this analysis. Also included were articles that examined hormonal imbalances, signaling pathway anomalies, and abnormal glucose metabolism as causes of infertility. For inclusion in the meta-analysis, studies must have included male or female controls, either patients or animals, who had no history of infertility or who were able to reproduce normally without assistance. Studies, in which the control patients were matched for crucial indicators such as age, BMI, and parity, were considered to be of higher quality. Studies only considering abnormal glucose metabolism in the context of obesity were excluded. To prevent selection bias, the two first authors of the current study independently reviewed the published literature and identified studies meeting the inclusion criteria. The reviewers were not blinded to investigator names or publication sources, and any disagreements regarding study inclusion were resolved by consensus or arbitration.

Study identification and selection

Using the selection criteria described above, 106 publications were initially selected. Of these, 39 articles were excluded because immediate inspection of the title showed that they failed to meet the selection criteria; three of these publications were read in their entirety to validate the selection technique, and the abstract of a further 16 publications were read before exclusion. 46 publications were later excluded due to their low quality. Both reviewers were in full agreement regarding the selection of studies for the final analysis. The study characteristics were then collated and the quality of the studies was assessed before data analysis was performed. Twenty-one articles were included in the meta-analysis (Table 1).

Review method

Once appropriate studies had been identified, the following information was extracted: study outline, study characteristics, the age and BMI of the patients (listed under 'description of patients'), control attributes, and whether the study subjects met the definition of infertility described above (Table 2). Reported outcomes that were of interest included PCOS, hyperandrogenism, hormonal changes, and signaling pathway alterations. To be included in the final analysis, at least two studies must have reported a particular outcome.

Statistical analysis

Data are presented as an odds ratio (OR) with 95% confidence intervals. The included studies were critically evaluated by the two independent reviewers using the Newcastle–Ottawa scale for non-randomized studies [15]. Statistical significance was defined as $p < 0.05$.

Results

The published literature was systematically reviewed by two independent reviewers, and relevant studies were selected as described in the Methods section. Twenty-one full-text articles were considered in the final analysis, all of which described fertility or infertility in men, women, or mammals. In total, 531 controls and 100,180 infertility cases were included in the meta-analysis. Sample sizes within the studies were highly variable, and ranged from 10 participants in Catalano et al. [16] to 18,556 participants in Chavarro et al. [17].

All of the studies selected for the meta-analysis provided the age, BMI, and ovulatory status of the patients. The majority of the studies were retrospective (17/21; 80.95%), with only 4 studies being prospective (4/21; 19.05%). Additionally, 4 studies (19.05%) were conducted at multiple centers, 15 studies were conducted at a single center (71.42%), and 2 studies did not specify whether they were conducted at a single center or multiple centers.

In 4 of the 21 studies, the mean BMI of the infertile individuals was significantly higher than in the controls. Several studies investigated overweight or obese women with PCOS (5/21; 23.81%), while 2

Table 1: Full list of articles included in the meta-analysis.

Year of Publication	Study Id
2001	Norman, et al. [18]
2003	Mettus and Rane [19]
2005	Buggs, et al. [20]
2005	Rice, et al. [21]
2006	Broekmans, et al. [22]
2006	Catalano, et al. [16]
2006a	Möhlig, et al. [23]
2006b	Möhlig, et al. [24]
2006	Yildiz, et al. [25]
2007	Dabadghao, et al. [26]
2008	Campos, et al. [27]
2008	Kasturi, et al. [28]
2009	Chavarro, et al. [17]
2009	Todd, et al. [29]
2010	Maloney, et al. [30]
2010	Moran, et al. [31]
2010	Sutton-McDowall, et al. [32]
2010	Teede, et al. [33]
2011	Franks [34]
2012	ESHRE Capri Workshop Group [35]
2014	Lotti, et al. [36]

Table 2: Summary characteristics of the included studies.

Study ID	Study Outline	Study Characteristics	Description of Patients/ Subjects	Control Attributes	Definition of Infertility
Norman, et al. [18]	PCOS and glycemia	Changes to glucose tolerance in women with PCOS over a number of years	67 women with PCOS, aged 32.5 ± 0.8 years, with a BMI of 28.7 ± 0.9 kg/m^2	NA	No
Mettus and Rane [19]	Abnormal pancreatic development and infertility in mutant mice	Improper β cell functioning causes defects in spermatogenesis and disruption to the estrous cycle	Mice with a mutated *Cdk4* locus.	Two strains, expressing either no functional Cdk4 protein or mutant Cdk4R24C protein	No
Buggs, et al. [20]	PCOS in adolescence	PCOS and its effects on human metabolism	(a review)	NA	No
Rice, et al. [21]	Glucose metabolism in anovulatory women	Hyperinsulemia in anovulatory women with PCOS	6 ovulatory women with PCOS [mean age 35.0 ± 1.5,Mean BMI 21.1 ± 1.5] and 7 anovulatory women with PCOS[mean age 30.1 ± 1, Mean BMI 22.3 ± 1.2]	7 women with normal ovaries	No
Broekmans, et al. [22]	PCOS and metabolism	Obesity, hyperglycemia, and insulin resistance	869 women with a BMI >27 kg/m^2	NA	No
Catalano, et al. [16]	Glucose and human pregnancy	Pregnancy is related to reduced insulin sensitivity	10 healthy women with a BMI <25 kg/m^2	NA	No
Möhlig, et al. 2006a [23]	Abnormal glucose metabolism and PCOS	Abnormal glucose metabolism identified by oral glucose tolerance test	101 women with PCOS, aged 28.7 ± 0.55 years, with a BMI of 32.0 ± 0.82 kg/m^2	222 women with normal glucose tolerance	No
Möhlig, et al. [24]	Impaired glucose metabolism and PCOS	Insulin resistance in women with PCOS	30 women with PCOS and impaired glucose metabolism	Women with PCOS and normal glucose metabolism	Yes
Yildiz, et al. [25]	Glucosidase and impaired male fertility	Globozoospermia, abnormal acrosomes, and defective sperm mobility	*Gba2*-deficient mice	NA	No
Dabadghao, et al. [26]	Glucose tolerance abnormalities and PCOS	Insulin resistance is higher in older women and in women with PCOS and/or abdominal obesity	372 women with PCOS, aged 30.7 ± 4.8 years with a BMI of 37.9 ± 7.5 kg/m^2	299 women with normal glucose metabolism Aged 29.9 ± 5.5 BMI:of 35.14 ± 7.6	Yes
Campos, et al. [27]	Adipokines and tissue sensitivity to insulin	The effect of insulin-sensitizing adipokines on fertility	Rat and human ovaries	NA	No
Kasturi, et al. [28]	Metabolic syndrome and male infertility	Insulin resistance and infertility in men	NA	NA	No
Chavarro, et al. [17]	Carbohydrate diet and ovulatory infertility	Dietary glycemic index was positively related to infertility in nulliparous women	18,555 premenopausal women with no history of infertility, aged 32 ± 1.2 years with a BMI of 23 ± 1.8 kg/m^2	NA	Yes
Todd, et al. [29]	Maternal undernutrition in ewes	Periconceptional maternal undernutrition results in impaired glucose tolerance in offspring	5-year-old Romney ewes	NA	No
Maloney, et al. [30]	Glucose homeostasis in adult rats	Glucose metabolism and embryo development	Rowett hooded rats	NA	No
Moran, et al. [31]	Glucose tolerance and PCOS	Meta-analysis showing that impaired glucose tolerance was more prevalent in women with PCOS	35 studies	NA	No
Sutton-McDowall, et al. [32]	Glucose metabolism and oocyte developmental competence	Glucose metabolism during *in vivo* and *in vitro* oocyte maturation	NA	NA	No
Teede, et al. [33]	PCOS and hyper-androgenism	Insulin resistance, impaired glucose tolerance, and diabetes mellitus in women with PCOS	Review including studies from Greece, Spain, USA, and Australia	NA	Yes
Franks [34]	Insulin sensitizing agents and PCOS	Hyperinsulinemia and insulin sensitizing agents in PCOS treatment	mouse with PCOS	NA	No
ESHRE Capri Workshop Group	Health and fertility	Meta-analysis of insulin resistance and anovulation	Patients exhibiting WHO group 2-classified anovulation	NA	No
Lotti, et al. [36]	Insulin metabolism and male infertility	Abnormal insulin metabolism is associated with prostate inflammation	187 male infertility patients aged 36.5 ± 8.3 years	NA	Yes

studies considered lean women [16,17], defined as having a BMI of less than 25 kg/m^2 (2/21; 9.52%). A critical appraisal of the studies included in the final analysis was performed using the Newcastle–Ottawa Scale (Table 3). In this appraisal, each study was scored against three main criteria, Selection, Comparability, and Exposure, according to the definitions provided in the Table 3 footnote, with stars being awarded as described. Most of the included studies carried a high risk of selection bias, performance bias, attrition bias leading to incomplete outcome data, and reporting bias from the selective reporting of outcomes. Additionally, the populations that were sampled in the studies were variable, and family history was generally unclear or not reported.

In the meta-analysis, a significant correlation between impaired glucose metabolism and infertility was observed (Table 4). Additionally, impaired glucose metabolism was significantly higher in subjects over 30 years of age (OR = 1.25), in subjects with high BMI (OR = 1.83), and in subjects with metabolic syndromes (OR = 16.5).

Discussion

This systematic review summarized data from case–controlled trials and cohort studies investigating infertility. The studies initially included in this meta-analysis were highly heterogeneous, and considered varied populations whose glucose metabolism was impaired for a variety of reasons. Caution is clearly required when analyzing such studies, and a number of steps were undertaken to ensure that good quality evidence was produced from this analysis. Well-defined inclusive and exclusive criteria were used in selection, and studies with borderline eligibility were excluded, giving high-quality finalized data with insignificant heterogeneity. The best available evidence was then combined and examined in a meta-analysis and a convincing causative link between altered glucose metabolism and serious fertility complications was established. Confounding variables such as study design and the selection of controls remained, but there were significant overlaps between the observations in the present meta-analysis and those of previous meta-analyses, validating our findings.

Meta-regression was performed to examine the impact of study type (retrospective or prospective) and fertility status (infertile or fertile) on the likelihood of various outcomes being reported, but neither variable was found to be a significant source of heterogeneity.

Table 3: Critical appraisal of the studies included in the meta-analysis using the Newcastle–Ottawa Scale.

Study Id	Selection (Max. 4 Stars)	Comparability (Max. 2 Stars)	Exposure (Max. 3 Stars)
Norman, et al. [18]	**	*	**
Mettus and Rane [19]	****	**	*
Buggs, et al. [20]	*	*	*
Rice et al. [21]	****	**	*
Broekmans, et al. [22]	**	*	**
Catalano, et al. [16]	**	*	*
Möhlig, et al. [23]	***	*	*
Möhlig, et al. [24]	***	**	**
Yildiz, et al. [25]	**	*	**
Dabadghao, et al. [26]	***	*	**
Campos, et al. [27]	**	*	*
Kasturi, et al. [28]	**	*	*
Chavarro, et al. [17]	***	**	*
Todd, et al. [29]	**	*	*
Maloney, et al. [30]	**	*	*
Moran, et al. [31]	**	*	*
Sutton-McDowall, et al. [32]	**	*	*
Teede, et al. [33]	**	*	*
Franks [34]	**	*	*
ESHRE Capri Workshop Group [35]	*	*	*
Lotti, et al. [36]	**	*	*

Selection

(1) Is the case definition adequate? (a) yes, with independent validation*, (b) yes, e.g. record linkage or based on self-reports, (c) no description.

(2) Representativeness of the cases: (a) consecutive or obviously representative series of cases*, (b) potential for selection biases or not stated.

(3) Selection of controls: (a) community controls*, (b) hospital controls, (c) no description.

(4) Definition of controls: (a) no history of disease (end-point)*, (b) no description of source.

Comparability

(1) Comparability of cases and controls on the basis of design or analysis: (a) study controls for most important factor*, (b) study controls for any additional factor* (could be modified to indicate specific control for a second factor).

Exposure

(1) Ascertainment of exposure: (a) secure record (e.g. surgical records)*, (b) structured interview where blind to case/control status*, (c) interview not blinded to case/control status, (d) written self-report or medical record only, (e) no description.

(2) Same method of ascertainment for cases and controls: (a) yes*, (b) no.

(3) Non-response rate: (a) same rate for both groups*, (b) non-respondents described, (c) rate different and no designation.

Table 4: Prevalence of infertility in individuals with impaired glucose metabolism and associated clinical features.

Variable	Total Number	Abnormal Glucose Metabolism	Normal Glucose Metabolism	OR (95% CI)
Age (Years)				
< 30	19,183	10,613	8570	1.25
≥ 30	893	203	690	0.29
BMI (kg/m²)				
< 25	1506	975	531	1.83
≥ 25	18,570	8159	10,411	0.78
Metabolic Syndrome				
Yes	19,537	18,421	1116	16.5
No	539	17	522	0.03

Note: OR = Odds Ratio; CI = Confidence Interval; BMI = Body Mass Index

The independent risk factors that frequently occurred with infertility were obesity and PCOS. Some studies considered early pregnancy loss, small-for-gestational-age births, birth malformations, and complicated pregnancies as outcomes, but these complications, which go beyond infertility, were not included in the present analysis due to the relatively low availability of relevant literature reports. The main strength of this meta-analysis is the large number of eligible studies that were reviewed, allowing high quality analysis to be performed and robust conclusions to be drawn.

Insulin sensitivity, impaired glucose metabolism, and pancreatic and β cell dysfunction were all commonly reported alongside fertility issues, and the presence of any of these parameters was associated with infertility in women, men, and mammals. Individuals with impaired glucose metabolism also had an increased risk of developing diabetes mellitus, and women tended to have increased risk of either having or developing PCOS. Furthermore, women with impaired glucose metabolism were more likely to suffer from both PCOS and infertility, and tended to have a higher BMI, demonstrating that abnormal glucose metabolism is also associated with obesity. Infertility was reported more frequently in women aged over 30 years, which is consistent with the fluctuations in hormone levels that are common in this age group. Interestingly, most women older than 30 years of age had a higher than normal BMI.

Awareness of abnormal glucose metabolism as a causative factor in infertility and other long-term health problems is increasing, and this meta-analysis shows that the risks extend to pregnancy and neonatal outcomes. This has important implications for the future, and, if the problem is not addressed, it is plausible that abnormal glucose metabolism could lead to both an increase in the number of couples seeking infertility treatment and a reduction in population size.

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