Association of glucose-6-phosphate dehydrogenase (G6PD) expression and obesity: A systematized review

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ABSTRACT

Several studies have associated glucose-6-phosphate dehydrogenase (G6PD) overexpression with obesity due to its roles in proinflammatory signalling. However, a systematic review has not been reported to synthesize and evaluate the findings. This is a systematized, scoping review on the recent 10-year publications for all species, and all-time studies in humans on the associations of G6PD with obesity. Systematized electronic searches on Pubmed and Medline for all studies from April 2011 to April 2021 were performed; Pubmed was searched for all human studies. The eighteen human studies since the 1960s to date reported ambiguous, conflicting outcomes on the association of G6PD expression and weight regulation. Over the last ten years, however, the ten included reports for all species, which were primarily mice studies, all suggested that G6PD activity or level is increased in the obese. In the same way, G6PD deficiency has been linked with insulin resistance amelioration and weight gain reduction due to opposing mechanisms. In line with this, four of the included studies were diet inclusion or pharmacotherapeutic interventions to suppress G6PD activity, hence weight gain and obesity. Further investigations, particularly on pharmacotherapeutic applications on the roles of G6PD on obesity are needed.

Contribution of Authors

Esphie Grace Fojas – Conceptualization, data curation, methodology, writing – original draft

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ABBREVIATIONS

G6PD - Glucose-6-phosphate dehydrogenase

G6PDD - Glucose-6-phosphate dehydrogenase deficiency

NADPH – Nicotinamide adenine dinucleotide phosphate

NAM - Nicotinamide

PPP – Pentose phosphate pathway

ROS – Reactive oxygen species

RV – Resveratrol

INTRODUCTION

Obesity has risen to epidemic levels with continuously increasing prevalence worldwide regardless of a country's development status (1). In 2016, over 2 billion and 650 million adults were overweight and obese, respectively (2). Increased risk of various illnesses, primarily cardiovascular disease and type 2 diabetes (T2D) has been attributed to obesity (3), aggregating its impact on global health and economic burden. Obesity has also been associated with increased risk of severity for coronavirus disease 2019 (COVID-19) (4), a still on-going pandemic. Several preventive and treatment modalities have been proven to be effective to curb obesity (5); the most efficacious of which is bariatric surgery (BS). BS procedures have three general types, namely- restrictive, to curb consumption (e.g. gastric banding); malabsorptive, to reduce weight via digestive and absorptive interferences (e.g. intestinal bypass); and mixed methods, both restrictive and malabsorptive (e.g. gastric bypass) (6). However, BS has been linked with several complications and nutritional deficiencies (7, 8). Nonetheless, there is a pressing need for further investigations on the pathophysiology and management of obesity.

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme vital for prevention of cellular oxidative damage; its deficiency (G6PD deficiency, G6PDD) being the most common enzymopathy (9). Over 400 million individuals in the world are G6PD-deficient (9, 10). G6PDD is primarily characterized by hemolytic anemia due to accumulating reactive oxygen species (ROS) which may arise from stress, food such as fava beans, or medications (10). G6PDD follows an X-linked inheritance pattern hence predominantly manifests in males (11).

Obesity is characterized by adipose tissue inflammation, which in turn is associated with ROS build-up due to oxidative stress (12). G6PD, the rate-limiting enzyme in the pentose phosphate pathway (PPP) which is the vital source of cytoplasmic NADPH (13), has been shown to be increased in adipose tissues of obese animals (14). Investigations amongst humans are limited and contradictory with the earliest report appearing to be in the 1960s (15, 16). The effect of diet therapy on G6PD activity have been studied in the earlier years (17-20) and the effect of physical activity has been investigated amongst patients with Down Syndrome in 2005 (21). In 2012, the effect of a BS type on G6PD activity in patients with obesity and Type 2 diabetes was examined (22). Most of the studies on G6PD

expression and its effects on adiposity over the last decade have been on mice or rats (10, 13, 14, 23-28). Collectively, these animal studies, and others (12, 22, 29, 30), suggest strong correlation of G6PD overexpression to adipose tissue expansion in obesity. In the same way, G6PDD has been shown to have potential protective roles against obesity and insulin resistance (10, 25), as well as T2D (22) and cardiovascular disease (13).

This paper aims to review relevant publications for all species on the association of G6PD and obesity In addition, this study aims to further focus on human studies for clinical applicability. Evaluating the latest reports involving different subjects combined with the relevant available body of knowledge on humans in this systematized review may prove beneficial to provide outcome implications and ensuing research recommendations.

Search

The search strategy was performed using Pubmed for human studies, and Pubmed and Medline databases for recent 10-year studies. The following terms were used to search in titles and abstracts or as Medical Subject Headings with Boolean operators: "G6PD," "G-6-PD," "G6PD deficiency," "G-6-PD deficiency," "G6PDD," "Glucosephosphate dehydrogenase," "Glucosephosphate dehydrogenase deficiency," "BMI," "body-mass-index," "body weight," "bodyweight," "body mass index," "obesity," "adiposity," obes*, adipo*, and "humans".

A filter to include studies in the recent 10 years to take into account current advancements in technology for all subject types was used. The time filter April 2011-April 2021 was selected to exclude potential effects of COVID-19 infection (started Dec 2019) and taking into consideration the median time frame of 14 months from research project development to publication (31) (i.e. up to April 2021); articles were last searched on 25 April 2021. Duplicated studies from Pubmed and Medline were checked, as applicable. Subsequently, to ensure that the search was current, all human studies from Pubmed were added for this scoping review, with no time filter; articles were last checked on 28 June 2023. Researcher [EF] thoroughly checked the results.

Selection

The inclusion criteria were observational studies (eg. cohort, case reports, case series, cross-sectional, case control), experimental investigations (e.g. genetics, clinical, experimental, quasi-experimental, in vitro, cell studies, interventional), and other relevant publications. Only publications in English were included.

Obesity was defined as body mass index (BMI) of over 30 kg/m^2 (2); adiposity as accumulation of adipose tissue or body fat deposits (32); and body weight as a subject's total mass or weight. Outcome measures included effect/s of G6PD deficiency/defect/mutation/activity/expression on obesity or weight in relation with BMI, insulin resistance, adipose tissue or adipose tissue inflammation, adipocytes, oxidative stress, fatty acids inflammatory signals, glucose uptake, or medical/pharmaceutical or other interventions which include direct effects on G6PD activity/expression and obesity/weight. Studies with or without comparators were included.

Studies which did not directly include the association of obesity, adiposity, or weight regulation with G6PD or G6PDD, letters to the editor, commentaries, and similar publications were excluded. Reports which discuss obesity comorbidities such as diabetes, cancer, and cardiovascular disease, were only included when obesity in relation to G6PD has been integrated.

Data extraction and synthesis

Selected studies were appraised. A standard template table was designed by the researcher for data extraction. Primary information retrieved in each study included reference (authors and year of publication), study design, subjects (animal or others), number of subjects (N), relevant results as outlined in the 'Selection,' outcome measures, summary of findings, and study conclusions. Due to different types of studies included in this review, and it being a systematized review, overall quality of evidence was not evaluated. The results from the included studies were compared and summarized.

Included Studies

This section identifies the number of articles that were included in this study based on the selection criteria, specifying the total number of publications retrieved, excluded, and the final numbers included.

For the inclusive human studies, Pubmed search generated 132 publications. After scrutiny of the titles/abstracts, 25 articles were found potentially relevant. Of these, 5 reports were not included due to unavailability or irretrievability. Two studies did not meet inclusion criteria on further evaluation; thus, 18 studies were included (Figure 1).

For the recent 10-year publications for all species, search from the two databases yielded a total of 214 (Pubmed=147; Medline=214) studies based on the terms and Boolean operators used. After excluding duplicates, the articles' abstracts were screened by the researcher. Thirteen studies were found relevant. However, full text of 2 articles could not be retrieved (1 was in Chinese) and 1 was a commentary- these were excluded. Hence, application of inclusion and exclusion criteria generated a total of 10 studies (Figure 2).

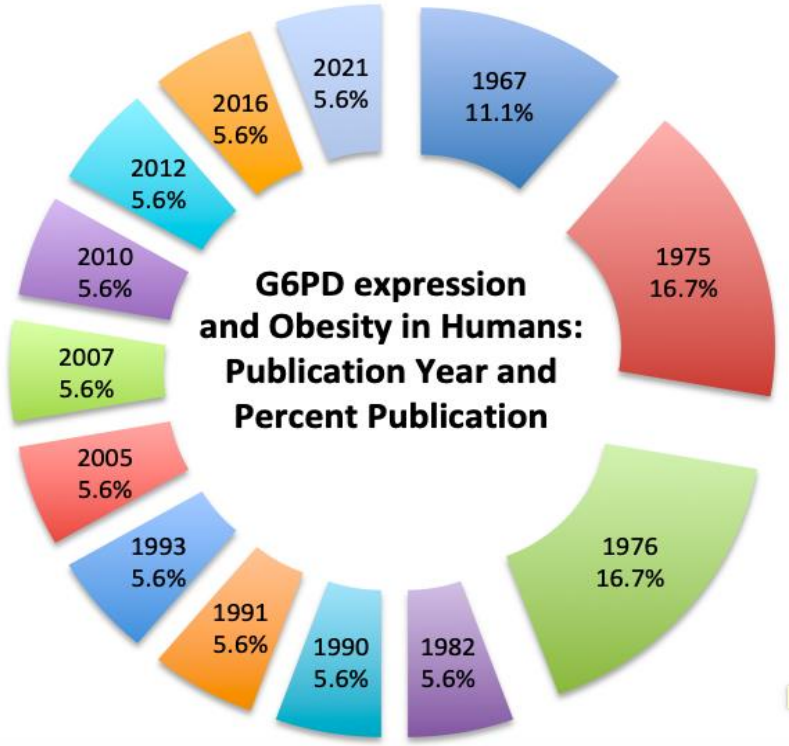

Figure 1. Publication distribution on the association of G6PD expression and obesity in humans.

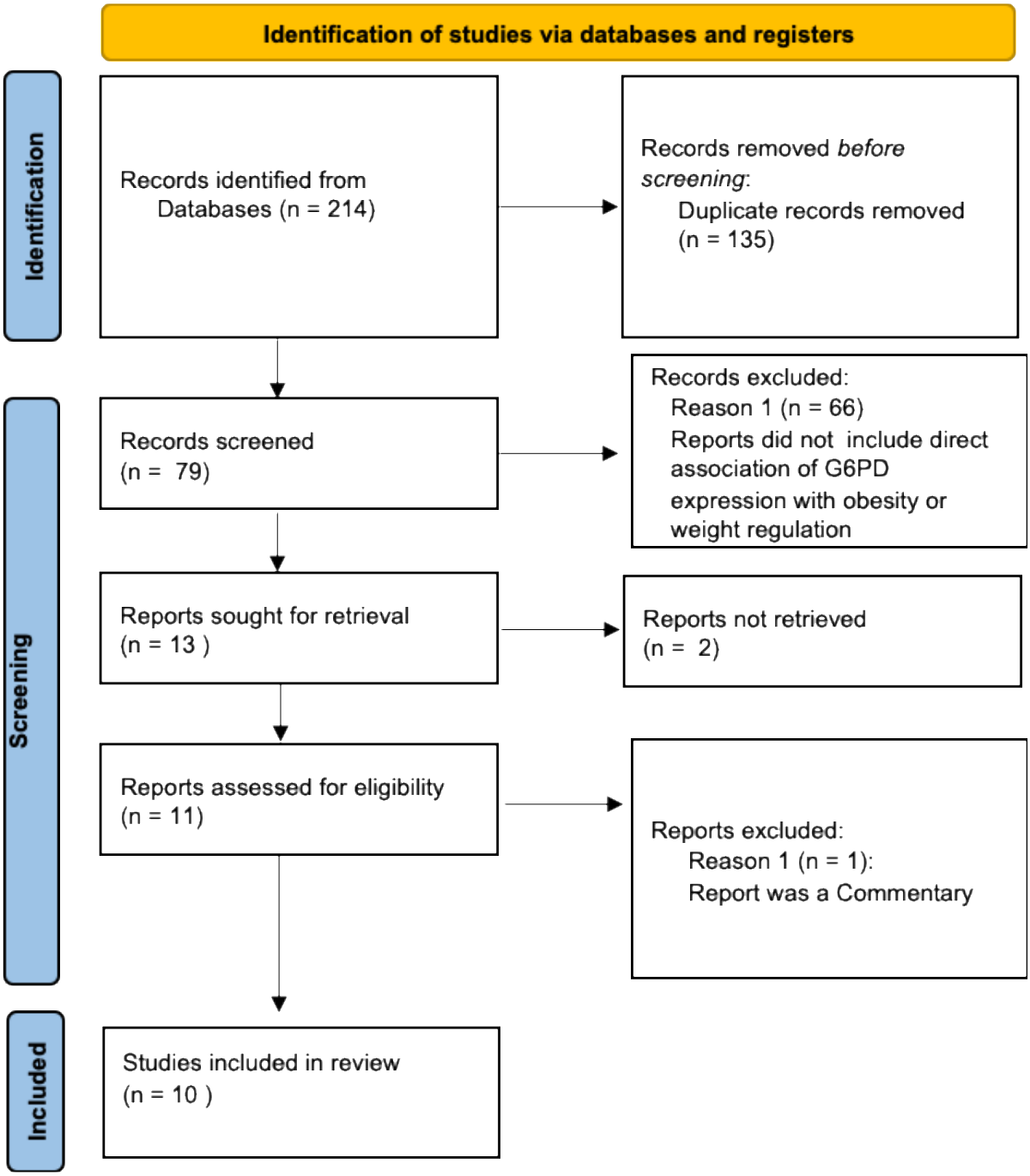

Figure 2. Flow chart showing the study selection process for all species in the recent 10 years. Identification, screening, and selection of articles based on inclusion criteria on the association of G6PD with obesity for publications from April 2011-April 2021 using two databases.

Study characteristics

This section defines relevant characteristics of the included publications in the study.

For the 18 human-specific studies (15-22, 25, 33-41), publication range was 1967-2021. Nearly 50% of the studies were from the 1960s to 1980s; two studies (22, 25) were from the recent decade.

From the total of 10 included studies in the current 10 years, eight involved the use of animals, 7 (10, 13, 14, 23-26) of which were on rats or mice and 1 (29) was a study on fish. One study was solely on humans (22). The settings of the 10 studies were from 6 countries: 3 from Korea, 2 from USA, 2 from Mexico, and 1 each from Australia, Spain, and China. Two of the 3 Korean studies and both studies from the USA were from the same group. The reports were published between 2012-2018.

G6PD expression and association with obesity

In this section, relevant association of G6PD expression with obesity from the included studies are described and elaborated.

The results of the human studies were widely varied and opposing. In 1967 alone, one study postulates that higher G6PD activity associates with lower body weight (16), while another's (15) report was contradictory. The effect of caloric restriction to G6PD activity was not significant for one study (18), but appeared to reduce G6PD activity for three other studies (17, 19, 20). Similarly, studies involving patients with diabetes had varying outcomes with regard to G6PD activity (22, 34, 39). Summary of the included studies on humans is presented in Table 1.

For the recent publications, all ten studies suggest that G6PD activity or level is increased in the obese, and its expression or overexpression associates with increasing BMI and lipogenesis due to oxidative stress or chronic adipose tissue inflammation (10, 13, 14, 22-26, 29, 30). In the same way, G6PD defect or deficiency has been linked with insulin resistance amelioration and weight gain reduction due to opposing mechanism. Four of the studies were diet (23, 24) or pharmacotherapeutic (26, 30) interventions which suppress G6PD activity to curb weight gain or obesity. Resveratrol was the dietary inclusion investigated, while nicotinamide was the medication evaluated. Both have been shown to be effective for reduction in weight due to mechanistic effect of G6PD activity suppression on weight regulation (23, 24, 26, 30). Summary of the included studies is presented in Table 2.

Reference	Conclusion/s
Tjabbes, et al., 1967[16]	Negative correlation between fatty tissue G6PD activity and relative body weight
Lopez-S, et al., 1967[15]	Positive correlation between G6PD activity and percentage excess body weight
Belfiore et al., 1975[34]	In adipose tissue, higher G6PD activity observed in normal tissue compared to diabetic tissue
Willgerodt, et al., 1975[41]	In adipose tissue, significantly higher G6PD activity observed in newborns compared to infants and adults
Beiul, et al., 1975[17]	After diet intervention, decreased body weight corresponded to significantly increased fatty tissue G6PD activity
Belfiore, et al., 1976[18]	G6PD activity unchanged after 15 days of normal caloric intake and balanced diet
Oleneva, et al., 1976[19]	Decreased G6PD activity on fatty tissue after diet therapy irrespective of age
Belfiore, et al., 1976[33]	Adipose tissue G6PD activity markedly decreased in non-obese diabetics compared to controls, but unchanged in obese diabetics
Timmers, et al., 1982[20]	Significantly lower G6PD activity in adipose tissue observed after 7 days of severe caloric restriction
Moghetti, et al., 1990[37]	Although statistical difference was observed in other enzymes involved in glucose metabolism, no reported significant difference for G6PD activity in mononuclear blood cells versus typical insulin target tissue in 15 non-diabetic obese women
Monte Alegre, et al., 1991[38]	Between 12 men with G6PD deficiency and 11 normal: no significant difference in plasma glucose levels after intravenous (IVGTT) and oral glucose tolerance tests (OGTT); however, significantly lower insulin levels observed for G6PD-deficient subjects
Muggeo, et al., 1993[39]	In 77 obese subjects, the presence of diabetes associated with reduced G6PD activity
Ordoñez, et al., 2005[21]	In male adolescents with Down Syndrome (31 subjects), G6PD increased significantly after 12-week physical activity program compared to baseline values

Park, et al., 2007[40]	Suggest G6PD as a novel target for treating metabolic disorders in relation to its role in the induction of obesity-associated oxidative stress
Mailloux, et al., 2010[36]	G6PD as an important source of NADPH in mitochondria, wherein glucose availability and differences in metabolic state modulate enzymatic sources of NADPPH
Schneider, et al., 2012[22]^	Higher G6PD activity in diabetics compared to non-diabetics. After Laparoscopic Roux-en-Y gastric bypass (LRYGB), G6PD activity observed to increase after 1 month and decrease after 3 months
Lee-Young, et al., 2016[25]^	Inverse association between G6PD activity and nitric oxide synthase (NOS) in skeletal muscles; reduced G6PD activity, increased NOS activity result to increased insulin-independent glucose uptake
Ceylan, 2021[35]	Hub genes (including G6PD) remarkably altered in patients with obesity and hepatocellular carcinoma

Table 1. G6PD expression and association with obesity in humans.
^also found in Table 2

Reference	Study Design	Subjects	Number of Subjects	Outcome Measures	Summary of Findings
Schneider, et al., 2012[22]	Case-control	Humans	N=16 (n=8 obese diabetic; n=8 obese non-diabetic)	Pre-operative correlation of G6PD activity in red blood cells (RBC) and BMI in obese diabetic and non-diabetic patients who underwent LRYGB	• A positive correlation was found between RBC G6PD activity and increasing BMI. • No correlation was observed between adipocyte G6PD activity and BMI.
Torres-Ramirez, et al., 2013[30]	Experimental	Mice cells	Not available	Evaluation of nicotinamide (NAM) as a G6PD inhibitor for potential pharmacotherapeutic applications against obesity	• G6PD activity and expression affect redox balance and lipid accumulation • NAM modulates redox balance and lipid accumulation by decreasing G6PD activity • Decreased G6PD activity due to NAM may be suggestive of potential therapeutic applications of NAM against obesity
Cho, et al., 2012[23]	Randomized controlled trial (animal)	Mice	N=40 male mice (randomized to: n=10 normal diet; n=10 high fat diet (HFD) + 0 resveratrol (RV); n=10 HFD + high RV; n=10 HFD +	Investigation on the effects of RV diet inclusion on G6PD suppression to aid in the prevention of diet-induced obesity (DIO)	• The activity of G6PD was observed to be decreased in mice fed with low dose RV compared to mice fed with high fat diet alone. • Low-dose RV may be an effective dietary inclusion to help combat DIO.

			low RV)		
Hecker, et al., 2012[13]	Experimental case-control	Mice	N=120 female mice (n=60 homozygous mutant G6PD mice (G6PDX); n=60 wild-type (WT) control mice)	Investigation on the effect of G6PD deficiency on weight gain due to obesogenic diet by evaluating G6PD activity	• G6PD activity was found to be reduced in the heart, liver, and skeletal muscles of G6PDX mice compared with the WT mice • G6PD deficiency resulted in lesser weight gain due to high fat or high caloric intake.
Gomez-Sorita, et al., 2013[24]	Randomized controlled trial (animal)	Rats	N=20 male rats (2 groups; n=10/group, 11 group as control)	Evaluation of RV as a therapeutic instrument to address adipocyte inflammation markers, such as G6PD, and body fatness hence combat obesity in genetically obese rats	• Significant reduction in G6PD activity was observed with treatment of RV • Without modifications in food consumption, significant reduction in weight was observed in RV-treated rats • Weight of adipose tissue was reduced in RV-treated rats; however, this was not statistically significant
Ham, et. al, 2013[14]	Quasi-experimental	Cells, mice, humans	N, mice=not specified N, humans=70 Japanese (n=32 men; n=38 women)	Demonstration of macrophage G6PD roles as regulator of oxidative stress and proinflammatory signals resulting to adipose tissue expansion in obesity	• Macrophage G6PD expression is more elevated in obese subjects • Macrophage G6PD expression is stimulated by lipopolysaccharides and free fatty acids and regulates expression of proinflammatory

					cytokines • Macrophage G6PD causes augmentation of oxidative stress, and mediates inflammatory gene expression as shown by stimulation of p38 mitogen-activated protein kinase (MAPK) phosphorylation
Ham, et al., 2016[10]	Experimental	Cells, mice	Not available	Elucidation on the effects of G6PD deficiency on chronic inflammation and insulin resistance in obesity due to diet	• G6PD defect was associated with insulin resistance amelioration in DIO • Oxidative stress and chronic inflammation reduction in obese adipose tissue were observed in G6PD-deficient mice
Lee-Young, et al., 2016[25]	Experimental	Cells, mice, humans	Not available	Examination on the role of G6PD activity on the development of insulin resistance in skeletal muscle	• This is a novel finding on the role of G6PD on glucose uptake in skeletal muscle • G6PD activity was found to be 45% increased in skeletal muscle of obese mice during fasting
Mejia, et al., 2017[26]	Randomized controlled trial	Mice	N=30 (randomly distributed to 6 groups including	Evaluation of the effect of NAM on G6PD expression in mice fed with chronic and high sugar intake	• G6PD protein, mRNA, and activity were reduced with the administration of NAM • NAM reduced oxidative and

			control, glucose, glucose + different concentrations of NAM, fructose, and fructose + varying concentrations of NAM)		inflammatory stresses as well as weight gain
Jiang, et al., 2018[29]	Randomized controlled trial (animal)	Fish	N=160 (n=20 randomized fish/tank; 8 tanks)	Characterization of full-length G6PD cDNA of *Megalobrama amblycephala* or blunt snout bream and response to sugar intake levels	• High carbohydrate feeding significantly increased G6PD expression and activity, as well as lipid contents in liver and adipose tissue • Stimulation of the pentose phosphate pathway and lipogenesis were indicated due to increased high caloric intake

Table 2. G6PD expression and association with obesity: Summary of studies in the recent 10 years.

DISCUSSION

The reports on human studies from all time on the association of G6PD expression and body weight regulation are evidently conflicting, thereby providing ostensible confusion rather than a concrete framework on the topic. Furthermore, the total publications appear low at 18 studies reported, which may imply lack of interest in the subject in humans. In addition, although different aspects of G6PD have been investigated, this has not included comorbidities such as diabetes and physical activity or diet intervention, but included probable effect of ageing (41) and the most common chromosomal defect, Down Syndrome (21). Further studies are required to be able to derive deductions of clinical use regarding the association of G6PD expression and obesity amongst humans as experimental animal studies are also not directly comparable to human studies primarily due to differences in metabolic characteristics. Furthermore, the difference in cell or tissue types studied (eg. adipose, erythrocyte, skeletal) present additional challenge to deriving conclusions.

On the other hand, the similar results from all the ten included studies amongst all species in the recent 10 years contribute to the strength of the reported associations between G6PD expression and obesity. Although the report of Schneider, et al., 2012[22] showed positive correlation of BMI with RBC G6PD activity only and not with adipocyte G6PD activity, the authors have provided a positive explanation that this could be attributed to the higher G6PD level in the whole body particularly in the blood since there is no difference in G6PD adipocyte concentration but the mass of total fat is elevated due to aggravating obesity (22).

The commentary (12) which was excluded in the selection process due to its nature, provides a succinct explanation on the roles of G6PD in obesity due to adipose tissue inflammation. The production of NADPH and ribulose-5-phosphate is vital for many cellular metabolisms, and with G6PD as the rate-limiting enzyme in the PPP, its importance is further emphasized on the mechanistic outcomes leading to obesity and systemic insulin resistance (12).

Limitations of the review and included studies

An obvious limitation of the study is the systematized and scoping nature which was performed by only one researcher. This calls for further investigations in

humans in different ethnic groups, age, and sex even though G6PD deficiency follows an X-linked inheritance pattern. In this light, the study of Hecker, et al., 2012[13] may in fact be questioned due to the use of female rats only. In addition, additional different evaluations on several tissue types may be included and compared as not many of the included studies incorporated this factor. More importantly, how the results of the mice studies translate to applications in humans is crucial.

As for the review process, a limitation worth considering is the apparent unfeasibility of performing a meta-analysis with the current available evidence, given the afore-mentioned wide range of variability in outcome measures of the included studies. This is true even for the included studies on mice or rats. Although the quality of the evidence appears strong, these are considerable issues which may be addressed by further larger and more comprehensive investigations including a wide-ranging systematic review.

Implications in practice

The therapeutic implications of the results of the findings are strong. Two of the potential candidates have already been included in the study: NAM (26, 30) and RV (23, 24). NAM is a G6PD non-competitive mixed inhibitor and has been shown to alter redox reaction, lipogenesis, (30) and hence fat accumulation and obesity. RV, on the other hand, is a naturally-occurring polyphenol normally found in plants such as grapes which has also been shown to combat DIO (24). These studies, however, were mice studies and certainly require further investigations particularly in humans; randomized controlled trials may warrant stronger confirmatory evidence. Another potential therapeutic agent reported was dehydroepiandrosterone or DHEA, also a G6PD inhibitor, which has shown efficacy in genetically obese rats (13). Nevertheless, advanced investigations on these candidates may be potentially worthwhile considerations. In addition, the implications on the role of G6PD in insulin resistance may be taken further than its effects on obesity to other cascades of diseases such as the metabolic syndrome, type 2 diabetes, and cardiovascular disease which the other included studies also already integrated.

CONCLUSION

Although conflicting studies on humans were published through the years, this review presented that in the recent years, there may be positive association of G6PD with adipose tissue inflammation and obesity, with bidirectional repercussions- G6PD defect or deficiency may associate with reduced weight gain and amelioration in obesity. The similarity in the results of all the included ten recent studies appears to provide strong quality of evidence, although further studies are certainly required. Implications in practice highlight the need for a systematic review, further investigations of biochemistry and pathophysiology involved, particularly in humans; and more importantly, therapeutic propositions.

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