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Pesticides and Risk of Obesity and Diabetes Risk: A Literature Review

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Abstract

Objective: This study examined current research evidence and literature linking pesticide exposure with obesity and diabetes.

Study Design and Setting: A literature review was conducted to summarize research studies regarding the association between pesticides and obesity, including both diabetes and metabolic syndrome. Published original research and review literature manuscripts were reviewed between 1996 and 2016.

Results: This summary reveals that majority of studies investigating an association between pesticides and obesity and/or diabetes have a positive correlation between pesticide exposure and key measures of diabetes and the metabolic syndrome, More specifically, pesticides are associated with body mass index, weight, glycated hemoglobin (Hemoglobin A1c), blood glucose and serum insulin levels. However, inherent complexities of pesticide chemicals and the multifactorial nature of obesity and diabetes may further limit this review's conclusions.

Conclusions: The literature supports a potential positive association(s) between pesticide exposure and obesity and/or diabetes. However, mechanisms accounting for such an association have yet to be defined, and notable gaps exist in assessing the extent to which an association may exist. Therefore, evidence supports further research to better define associations between pesticides and obesity disorders.

Abbreviations

AHS	:	Agricultural Health Study
BMI	:	Body Mass Index
DDE	:	Dichlorodiphenyldichloroethylene
DDT	:	Dichlorodiphenyltrichloroethane
MB	:	Methanobacteriales
OC	:	Organochlorine pesticides
OP	:	Organophosphate pesticides
PCBs	:	Polychlorinated biphenyls
POPs	:	Persistent organic pollutants

Keywords: Diabetes; Metabolic Syndrome; Obesity; Pesticides

Introduction

Several hundred pesticides have been used for centuries throughout various civilizations, yet their effects on human health remain poorly understood. Each pesticide has different mechanisms of action, uptake characteristics, metabolic effects, and elimination features; likewise, each has varying toxic effects on human health.. Over the last few decades, associations between health and certain pesticides have been identified. [1]. Associations between pesticides and neurologic function, immune system function, and endocrine function are increasingly being reported, and these findings help establish foundations for theories postulating how these chemicals may trigger human disease entities. This review

focuses specifically on the association between pesticides obesity and diabetes mellitus (DM) [1].

By definition, pesticides, including herbicides and insecticides, are substances used with the intention to prevent, destroy or control pests; pests are defined as vectors of disease or unwanted species of plants or animals hindering reproduction [2]. Pesticides are typically classified on their chemical structures and/or properties. For example, organophosphate (OP) pesticides, which are commonly used today in many insecticides, share a common mechanism of action through the disruption of acetylcholinesterase activity [1]. Organochlorine (OC) pesticides, lipophilic, chlorinated molecules, represent persistent chemicals in the environment of which many have been shown to be associated with serious human health problems [3]. Other pesticides fall into other groups such as bio-pesticides which are derived from animal, plant, and bacterial sources. And still others, like carbamates and pyrethroids, are unique in their formulations and structures and are classified in separate categories [4].

Over the last three decades, obesity prevalence among children and adults has reached almost epidemic proportions with nearly one-third of adults identified as being obese, and the literature shows pesticides may have a role in the pathogenesis of obesity [2,5]. Likewise, the number of adults diagnosed with DM has increased in number as well. Currently, more than 11% of the U.S. adult population suffers diabetes, and more than 35% have prediabetes. Noteworthy is the fact that in 2015 in the United States, 9.4% (about 30.3 million people of all ages) had diabetes in which about 70% of diabetics were either overweight or obese population [1,6].

Given these statistics, the rapid increase in the percentage of the population suffering both obesity and diabetes raises concerns about environmental causes. For obesity, dietary and physical activity changes can be attributed as causative agents to a degree, but exposure to environmental chemicals, including pesticides, have not been investigated as rigorously and can't be ignored. Type 2 DM risk increases with poor diet and physical activity levels, and pesticides have been shown to result in elevated glucose levels, insulin resistance, as well as concurrent hepatic changes which also heighten the risk for developing diabetes [1].

The objective of this literature review examined current research evidence supporting the role pesticides may have in advancing obesityand DM.

Materials and Methods

In this review, we summarized original research studies and literature review publications regarding the association between pesticides and obesity, including DM, the metabolic syndrome, and obesity.

Pesticides and Obesity

We searched various databases using a select group of keywords representative of pesticides and obesity. Relevant literature pertaining to studies from 1996-2016 were reviewed via abstract assessment. The specific databases used for this review included Google, Google Scholar, PubMed/NCBI, EBSCO (Academic Search Premier), SAGE, ELSEVIER, and Questa. Keywords used for reviewing the association between pesticides and obesity included pesticides, obesity, overweight, chlorines, organophosphates, adiposity, environmental chemicals, weight gain, and weight loss.

Pesticides and Diabetes

The literature review process involved a widespread search of the aforementioned databases using a select group of keywords representative of pesticides and DM, both Type 1 and 2 [7]. While randomized trials and systematic reviews were favored, all relevant literature pertaining to the subject between 1996 and 2016 were reviewed through abstract assessment. Keywords for searching the literature specifically included pesticides, diabetes mellitus, diabetes, hyperglycemia, organochlorines, organophosphates, environmental chemicals, insulin resistance, and blood glucose.

We describe relationships of different pesticide categories and obesity and DM based on their distinctions. Different theoretical considerations about mechanisms of pathogenesis are also presented. Likewise, we identify key gaps in research to enhance future research efforts in this area. We also present plausible conclusions that can be made about our current understanding of pesticides and their role in specific human health conditions.

Evidence of Pesticide Exposure and Obesity Risk

Organochlorine (OC) Pesticides and Obesity Risk

Organochlorines are lipophilic in nature and are naturally stored in fatty adipose tissues within the body following exposure. While most OC pesticides have been banned for use in the U.S. and other countries, many OCs persist in the environment. In addition, bioaccumulation of OCs among top-of-the-chain species occurs which poses ongoing human health risks [3]. Research has demonstrated that persistent organic pollutants (POPs), of which the majority is OCs, remain present in over 80% of the population today despite their elimination from use for nearly four decades [8]. Therefore, the potential for OCs in causing detrimental health effects remain.

The literature links OC pesticide exposure with obesity risk. Wei and colleagues demonstrated a dose-dependent effect of dicholorophenols in relation to obesity among adults after adjusting for age, gender, race, education, total fat intake, and physical activity [9]. Likewise, large national health and nutrition surveys

in both the United States and France have shown concentrations of certain OC pesticides to be higher as body mass indices (BMIs) increase in adult subjects [8,9]. Other studies have found a positive link between OC metabolites and childhood obesity [9]. Each study reviewed supports positive association between OCs and obesity.

While the association is noteworthy, causation has yet to be well established in the literature. Questions remain regarding whether OC pesticide levels are higher among obese individuals because of increased storage within adipose tissue or whether OC pesticides contributes to the causal chain in the development of obesity. Hue and coworkers demonstrated the concentration of POPs and OCs measured per gram of adipose tissue between obese subjects and lean controls were comparable suggesting obese individuals have higher OC pesticide levels due to greater volumes of adipose tissue [10]. Notably, however, another study showed that dramatic weight loss in obese subjects resulted in a rise in serum POP levels over 6 to 12 months as adipose tissue declined, on average, by 15% [11]. Weight loss associated with a rise in serum OC pesticide levels was supported in another study of 39 obese subjects placed on a hypo-caloric diet. Five of 26 OC pesticides (19.2%) measured showed statistically significant rises in serum glucose level in these subjects when compared to lean controls [3]. In summary, while most of the literature supports a positive correlation between OC pesticide levels and BMI, the association may simply be reflective of the OC pesticides' lipophilic nature and more adipose tissue among obese individuals, in which these chemicals can be biologically stored.

Other Pesticides and Obesity Risk

In addition to research involving OC pesticides and obesity risk, other groups of pesticides have also been studied in relation to weight changes but to a much lesser extent. Specifically, OP pesticides, being non-lipophilic in nature, have received less attention. However, a relevant study associating the OP pesticide chlorpyrifos and weight gain in rats deserves notice. Meggs and colleagues performed serial weight checks among rats injected with low-level chlorpyrifos as well as controls over a four-month span. At each serial assessment, injected rats gained statistically significant amounts of weight compared to controls, and the weight gain was attributable to additional adipose tissue and no other organ enlargement [12]. Although animal studies can't be generalized to humans, they do provide the scientific community with biological theories [13].

Other categories of pesticides have been evaluated infrequently in relation to obesity risk. Triclosan, a phenolic biocide used to control bacteria and fungi, exists in numerous consumer products including toothpaste, cleaning supplies and soaps. Approximately 75% of the population demonstrates detectable levels of triclosan metabolites in their urine. Data from the National Health and Nutritional Examination Survey from 2003 to 2008, researchers have shown that detectable triclosan levels are associated with a 0.9-point increase in BMI [13]. While these few studies support a relationship between non-OC pesticides and obesity risk, the relationship between triclosan and BMI requires longitudinal studies.

Theoretical Mechanisms for Obesity Risk from Pesticide Exposure

The literature shows that several potential pathophysiological mechanisms have been proposed relating pesticide exposure to obesity risk. Among the most prevalent is the theory involving endocrine disruption resulting from the exposure to various pesticides [13]. Some researchers have suggested pesticides, both lipophilic and non-lipophilic, may affect thyroid hormone levels as well as the hypothalamic-pituitary-adrenal (HPA) axis resulting in changes in appetite, satiety, and food selection [9,14]. Another study suggested that a disruption of estrogen and testosterone functions in addition to disruption of thyroid hormone function may have a negative effect [13]. Environmental chemicals have been shown to negatively affect endocrine systems, supporting a theory connecting obesity to pesticide exposure [12].

Alternative and concurrent beliefs regarding the association between pesticides and obesity risk involve adipogenesis theories. It has been reported that by activating peroxisome proliferator-activated receptor gamma, immature adipocytes may be stimulated to further differentiate leading to progressive risk for obesity [9]. However, limited research of OP pesticides has failed to support this pathophysiological mechanism [12]. Another study postulated pesticides trigger diffuse inflammatory changes within the body via the immune system increasing the risk of obesity [15]. Obesity has been characterized as a chronic inflammatory state evidenced by higher levels of circulating inflammatory cytokines resulting from an activated innate immune system, [5] thereby representing another potential pathway for adiposity.

One additional intriguing theory suggests pesticide disruption of gut microflora. By disrupting existing intestinal flora, specific bacterial species associated with obesity may disturb access to the intestinal lining and replace existing flora [13]. In one study, Lee and colleagues examined 83 women for the presence of methanobacteriales (MB), a bacterium that prefers petroleum-based environments and has been linked to obesity, and the presence of OC pesticide exposure. Their results demonstrated high correlations between the presence of MB and OC exposures, and likewise, both BMI and waist circumference were significantly higher in women with MB present [16]. In essence, possible changes with intestinal micro flora, pesticides may potentially enhance weight gain and obesity risks via nutritional pathways.

Evidence of Pesticide Exposure and Diabetes Risk

Organochlorine (OC) Pesticides and Diabetes Risk

While examining the literature regarding OC pesticides and diabetes risk, associated conditions of insulin resistance, metabolic syndrome, altered glucose metabolism as well as Type 1 and Type 2 diabetes mellitus were considered. In existing reviews of POPs, of which the majority are OC pesticides, about 75 studies have examined the effects of OC, organ fluorine, and organ bromine pesticides relative to altered glucose metabolism and diabetes risk [1]. Of these, strong associations between diabetes and various OC pesticides were found, including Dichlorodiphenyltrichloroethane (DDT), Dichlorodiphenyltrichloroethane (DDE), and polychlorinated biphenyls (PCBs) [1]. Although each of the OC pesticides is no longer used, each of the aforementioned pesticides in the environment and in human beings due to bioaccumulation effects.

In addition to this summative review, Andreotti and colleagues have examined data from the Agricultural Health Study (AHS) which was a prospective study of cancer and other health outcomes in a cohort of licensed pesticide applicators and their spouses from Iowa and North Carolina between 1993 and 1997 [17]. With a sample of more than 33,000 participants, studies have found increased incidence of diabetes among agricultural workers using the OC pesticides aldrin, chlordane and alachlor [18]. Likewise, agricultural workers' wives also have heightened diabetes risk when exposed to dieldrin and 2, 4, 5-Trichlorophenoxyacetic acid [19]. Saldana and colleagues examining over 11,000 pregnant women within the AHS over the course of the study found a positive association between commercial exposure to 2,4,5-Trichlorophenoxyacetic acid and 2,4,5-trichlorophenoxypropionic acid and gestational diabetes (odd ratio = 2.2) [19]. To note, among pregnant women, gestational diabetes is known to be a risk factor for subsequent development of diabetes in later life [20].

Montgomery and colleagues provided some specific statistics for diabetes risk in relation to select OC pesticides via the AHS investigation [18]. They assessed 50 different pesticides, of which many were OC pesticides, seven OC pesticides were associated with increased risk for diabetes. The ones with the highest risk included heptachlor with a 94% increase in risk; chlordane with a 63% increase in risk, and, Aldrin, now banned in the US, with a 51% increase in risk [18]. Given the number of research studies examining OC pesticides and diabetes risk, and given the large population samples surveyed, the evidence of the association between exposure to a variety of OC pesticides and the development of diabetes is quite strong.

Organophosphate (OP) Pesticides and Diabetes Risk

Though less well studied in terms of DM, OPs have been evaluated in few studies. Of the studies reported, most have demonstrated positive correlations between OP exposure and diabetes risk. The principal reports studies have involved those using AHS data obtained from agricultural workers and their wives. Notably, OPs, dichloros and trichlofon have been identified as being associated with heightened diabetic risk among occupational workers in the AHS study. Increases odds were found for these OPs when examining both ever-use and cumulative lifetime use of these pesticides [18]. Using the same AHS dataset, other researchers examined the wives of agricultural workers who used or were exposed to pesticides, and supported an association between OPs and diabetes risk among these women; OPs specifically cited included fonofos, phorate and parathion [21]. Albeit minimal research, findings support some association between OPs and heightened diabetes risk when exposure was prevalent.

Agricultural workers also deserve comment in relation to OPs and diabetes risk. Raafat and colleagues evaluated almost 100 Egyptian farmers over a 20-year period measuring serum malathion levels, an OP, fasting blood glucose, and fasting insulin levels. Interestingly, higher levels of malathion were associated with evidence of higher levels of insulin resistance over time [22]. Another study involved a comparison of 187 agricultural farmers in Iran with OP exposure with the same number of controls, measured using fasting blood glucose and an oral glucose tolerance tests, demonstrated greater occurrence of diabetes among the farmers [23]. Again, these studies support a positive association between OPs and diabetes.

The only other remarkable research relating OPs to diabetes risk, pertained to examining pesticide exposure to the onset of gestational DM. Again, the AHS dataset was used with over 500 women identified as developing gestational diabetes during their pregnancies. Based on self-reported data from these women, several herbicides and insecticides were found to have a significant hazards risk for being associated with gestational diabetes [19]. Specifically, phorate and diazinon were two OP insecticides found among the seven total agents identified [19]. It is of import to mention that in this same study, only women reporting commercial use exposure had such a risk while those with home and gardening exposure did not [19]. This may suggest a dose-dependent effect in relation to this phenomenon.

Other Pesticides and Diabetes Risk

In addition to the major groups of OC and OP pesticides, relatively few compounds have received research attention in relation to diabetes occurrence. One such compound, however, included pyrethroids which are commonly used as insecticides. Hansen [24] and coworkers evaluated 116 pesticide sprayers with primary exposure to pyrethroids relative to 92 controls without pyrethroids exposure. Each participant had HgbA1C measures obtained with an abnormally high HgbA1C of at least 5.6%. Notably, 61% of sprayers had abnormal HgbA1C measures while

less than 8% of the controls were affected. These findings led the researchers to correlate cumulative pyrethroid exposure to the development of prediabetes [24].

The remaining literature is relatively scant concerning other pesticides in relation to DM risk. In a study conducted by Saldana and colleagues cited previously, carbofuran as well as atrazine and butylate were identified as being associated with higher gestational diabetes risk among farmers' wives exposed to commercial pesticides [19]. Laboratory studies of adipocytes have shown that tolylfuanid, a fungicide, appears to disrupt glucose regulation pathways via a glucocorticoid agonist effect [25]. While carbamate is well known to cause acute toxicity and affect acetylcholine neurotransmitter function, long-term effects in relation to diabetes risk have not been shown [18].

Theoretical Mechanisms for Diabetes Risk Associated with Pesticide Exposure

Depending on which class of pesticides are considered, varying degrees of research support exist linking these chemicals to diabetes risk. Among these studies, numerous theories have been proposed in terms of etiologic mechanisms, and some of these demonstrate positive associations. The most common explanation links various pesticides to insulin resistance; in terms of OPs, some researchers suggest these pesticides activate serine kinases resulting[22] in inhibitory phosphorylation of cellular enzymes; therefore, greater insulin resistance develops within cells [26]. Others have supported similar mechanisms of alterations in enzymatic processes which then cause metabolic changes and insulin resistance [19]. In terms of OCs, persistent organic pollutants in adipose tissue have been proposed to heighten insulin sensitivity and result in altered glucose-insulin homeostasis [11]. Yet, other pesticides, such as malathion and pyrethroids which are known to affect insulin response and glucose regulation, lack clear evidence of association with diabetes risk [22,24]. While research evidence supports the association of various pesticides with insulin resistance and impaired glucose-insulin regulation, clear mechanisms behind these findings are yet to be well defined.

Other possible theories in this regard relate to altered lipid metabolism and secondary hepatic effects. For example, POPs have been noted to raise hepatic enzymes, increase lipid levels and lead to liver dysfunction [11]. Several OCs have been associated with elevated hepatic enzymes and liver disease [27]. Also, OPs have been shown to increase glucose release from the liver while also altering lipid metabolism [21]. Though how these chemicals cause these effects are not clear - lipotoxicity and glucotoxicity resulting from hepatic dysfunction is commonly associated with Type 2 diabetes [18]. Therefore, it stands to reason that pesticide effects on the liver may underlie their association with diabetes risk elevation.

The aforementioned evidence reflects primary theories behind pesticides and diabetes associations, but additional studies exist and may have a role in explaining these associations, especially in particular pesticide situations. For example, the fungicide tolylfuanid may disrupt insulin sensitivity and lipid metabolism through agonist effects on glucocorticoid receptors while also promoting adipose cell differentiation [25]. Lasram and colleagues have suggested various pesticides may cause autoimmune reactions resulting in Type 2 diabetes development [26]. Additionally, oxidative stress and inflammatory causes have also been proposed via secondary effects on the pancreas, liver and beta-cells [23]. Each of the theories considered in the literature have valid rationales, and many have laboratory support at a minimum. As a result, exact mechanisms linking pesticides to diabetes are likely complex and vary depending on the exact pesticide used, inherent risk of the individual, and other environmental and lifestyle factors.

Discussion and Conclusions

Prior to the mid-twentieth century, the use of pesticides was relatively rare. But subsequent to World War II, the manufacturing and use of these chemicals increased dramatically [3]. Despite the discontinuance of many of these agents due to human health effects, in some instances, bioaccumulation and environmental persistence have resulted in these agents continuing to exert potentially toxic effects [3]. Addition, many health conditions during this same time have risen significantly in incidence suggesting environmental etiologies may be at least partially involved [2]. Two such conditions include obesity and diabetes.

The literature reviewed in this current discussion offers some important considerations related to pesticides, obesity and diabetes. Though not extensive, randomized trials and systematic reviews have been conducted to assess this relationship. The majority, as reviewed, demonstrate positive correlations between specific groups of pesticides with various measures related to either obesity or diabetes. These measures include weight gain, increases in body mass indices, and enlargement of waistline circumferences as well as abnormalities in fasting glucose levels, HgbA1C levels, fasting insulin levels, lipids, and hepatic function [8,11,16-18,21,22,24,25] Given this information, further research and investigations should be strongly considered to better understand these phenomena.

Unfortunately, efforts to explain areas where explanations are lacking are numerous when it comes to both pesticides and these two specific health disorders. First, the number of pesticides are in the hundreds, and while many may be classified according to common mechanisms of action, each has nuances in metabolism, bioavailability, absorption rates, protein binding, side effects and toxicities [2]. Second, biomarkers for these chemicals in the

human body have yet to be well developed making measurement of exposure challenging at best [1]. Third, additional problems relate to the conditions of obesity and diabetes since both are multifactorial disorders likely resulting from a complex interaction among numerous genetic and environmental factors [1]. Therefore, the degree to which pesticides may be etiologic, if at all, is difficult to prove. Combining these challenges with a lack of in-depth understanding of age-related changes in human metabolism, detailed immune system functions, glucose homeostasis, and endocrine system interactions, it is understandable why answers from the current research pursuits have been limited [1]. Not only are large samples of study participants required, but advancements in our understanding of these associations are also essential to better identify the relationship between pesticides, obesity and diabetes.

While limitations in the current literature exists concerning these topics, some important insights are noteworthy. First, high number of individuals exposed to pesticides in both developed and developing countries as well as their persistence within human beings may have bioaccumulation effects;[3,23] this observation is most notable with lipophilic pesticides such as OCs, but in several studies, both agricultural workers and their families appear to have high risks for all types of pesticide exposures [18,21,28] Without knowing the effects such pesticides have in relation to obesity, diabetes and other health conditions, this raises concerns specifically from an occupational health perspective.

Other significant observations are the commonality of many of the theories linking pesticides to both obesity and to diabetes risk. Endocrine theories ascribe pesticide effects on the hypothalamic-pituitary-adrenal axis, thyroid function and/or glucocorticoid receptors in accounting for these health conditions [8,9,14]. Immune and inflammatory theories link elevated cytokine levels, heightened oxidative stress, and altered gut flora as potential mechanisms [13]. Theories related to metabolism suggest dysfunctions in glucose homeostasis, liver function, adipose cell differentiation, and cellular functions resulting in insulin resistance may play a role [11,19,23,25,27]. Last, pesticide interference with various neurotransmitters have been proposed as a common pathway by which pathologic changes may occur [1]. Each of these has some support from the literature, and they likewise offer directions for ongoing research.

In summary, current literature supports some associations among numerous pesticides, obesity and diabetes mellitus. Many studies have utilized large sample populations, and some have utilized effective research methodologies and designs in this endeavor. However, challenges exist due to variability among pesticides, complexities related to obesity and diabetes, and a lack of adequate biomarkers and understanding of potential physiological systems [1]. The dearth of research between biomarkers and physiological systems will remain research challenges, but despite this, many potential theories relating pesticides to these disorders exist with supporting rationale. Given the rapid advancement of obesity and diabetes prevalence, and the widespread exposure of human populations to pesticides, efforts to further elucidate additional insights into these relationships should be pursued. Furthermore, building upon current theoretical frameworks and research evidence is essential to advance this understanding (Table 1).

Table 1: Summary of Overall Findings of Pesticides' Association with Obesity and Diabetes.

Summary:

What is new? An updated review summary of current literature examines the associations between pesticide exposures and two health conditions, obesity and diabetes.

Key findings: Majority of studies available support a potential association between pesticide exposure with the development of obesity and/or diabetes. However, research has significant gaps and limitations in defining mechanisms or causation and extent of an association.

Added knowledge: Current literature suggests pesticide exposure could play a role in the development of obesity and/or diabetes. Multiple theories of causation exist, including endocrine, metabolic, immune and neurotransmitter theories, but none have been validated to date.

Implications: Literature review supports further research in these areas to better define mechanism of causation and degree of risk between pesticide exposure with obesity and/or diabetes development.

Conflicts of Interest

None.

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