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ACETONE, THE THIRD KETONE BODY. III. DEGRADATION BY OZONE AND HYDROGEN PEROXIDE AND THE DEVELOPMENT OF DIABETES MELLITUS. A HYPOTHESIS

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ABSTRACT

In recent years there has been an interest in air pollution and its possible role in the etiology of diabetes mellitus. A large number of epidemiological studies have highlighted the adverse effects of air pollution on diabetes and include risk profiles for different exposure durations, types of study design, subgroup populations, and effects of air pollution components. Several pollutants are known: Particulate matter, Carbon dioxide, Nitrogen dioxide, Sulfur dioxide, Lead and Ozone. On the other hand, acetone is formed in the body from acetoacetate either from spontaneous decaboxylation or by acetoacetate decarboxylase. Acetone levels vary depending on many factors, such as infancy, pregnancy, lactation, physical exercise, dieting, starvation and alcohol consumption. Acetone has been considered as an inert or waste product, useful marker to diagnose diabetes or ketoacidosis, but acetone can also lead to hyperglycemia. As a primary metabolite of acetone, isopropyl alcohol is formed by alcohol dehydrogenase. Physicochemical and physiological studies have shown that acetone treated with ozone/UV or by using 2-^{14}C-acetone, yields similar intermediates including methylglyoxal. Methylglyoxal is an important precursor in the formation of advanced glycation end products. These products are related to the development of chronic diseases and aging. Since methylglyoxal can be also formed from carbohydrate, lipids and protein metabolism and hydrogen peroxide is formed in the body or ingested from commercial products, several diseases including diabetes mellitus can be developed. The progression of diseases can be enhanced by environmental ozone in urban areas highly polluted.

KEYWORDS: Air Pollutants, Acetone, Diabetes Mellitus, Hydrogen Peroxide, Methyglyoxal, Advanced Glycation end Products.

1. INTRODUCTION

The term pollution means what people produce in such quantities that it interferes with health or well-being.[1] Air pollution increases due to human activity, it is classified as: Natural pollution, Primary pollution and Secondary pollution. From a physical or chemical point of view, air pollution implies a degradation of its quality. In general, the air in an urban area is more polluted due to the high population density and the activity that it carries out. In the last decade, an increase in the amount of particulate matter (PM) in the air has been observed in urban communities with adverse effects on human health since pollutants contribute to the development of respiratory and cardiovascular problems with serious economic implications for society.[1] Here, the role of ozone on acetone degradation is discussed related to diabetes mellitus development.

2. AIR POLLUTANTS

Air pollutants are classified into 6 types: 1. Particulate matter ($PM_{2.5}$, PM_5, PM_{10}), 2. Carbon dioxide, 3. Nitrogen dioxide, 4. Sulfur dioxide, 5. Lead and 6. Ozone.

3. SOURCES OF POLLUTANTS

The main sources of air pollutants are: Coal combustion, fires, dust generation, industrial activity, land transport, diesel and gasoline combustion.[2]

4. HEALTH EFFECTS OF AIR POLLUTANTS

The effects of exposure to air pollutants are twofold; short-term effects and long-term effects. Short-term effects include respiratory and cardiovascular effects. Cardiovascular effects include myocardial infarction mainly in people who are at risk of exacerbation of heart failure and arrhythmias[3] and respiratory effects when there is risk of exacerbation of asthma or bronchitis. Long-term effects also include cardiovascular and expiratory problems. Cardiovascular problems include myocardial infarction, atherosclerosis, and blood coagulability. Expiratory problems include pneumonia, lung cancer, abnormal lung development, and the development of asthma.

From the reproductive point of view, there are various alterations such as preterm births and low birth weight. The increased risk of low birth weight has been associated with exposure to

various pollutants; $PM_{2.5}$, PM_{10}, nitrogen dioxide, and ozone in the first and last month. The concentration of these pollutants has seasonal trends generally it is higher in Spring and lower in Summer. Ozone concentrations are highest in the months of September and October, and are of the order of 65.72 μg / m^3 and 84.18 μg / m^3, respectively.[4] Delayed intrauterine growth, abnormal size at birth, and abnormal head circumference have also been reported.[5]

Pollution affects children, the elderly and people who carry out their activities outdoors since the synthesis of vitamin D is also affected by preventing the passage of ultraviolet rays, thus affecting the mineralized tissue. In children, pollution also affects both cellular and humoral immunity.[5] In general, in the long term, there is an increase in mortality.[6]

5. AIR POLLUTION AND DEATH FROM COVID-19

It was recently reported that people living in communities exposed to long periods of highly polluted air are more likely to die from COVID-19 or experience more severe outcomes from the disease.[7] An increase of only 1 gram / m^3 of fine particulate matter in the air was found to be associated with a 15% increase in the death rate from COVID-19. The study defined high pollution levels as levels of fine particulate matter ($PM_{2.5}$) above 13 μg / m^3 of air, much higher than the US average of 8.4[7]

6. AIR POLLUTION, INCREASED NOISE AND METABOLIC SYNDROME

It has been reported that there is a risk of developing metabolic syndrome with a concentration of nitrogen oxides of 2.29 parts / billion caused by traffic, which causes a 15% decrease in the concentration of high-density lipoproteins and a 17% decrease from noise pollution of 11.6 decibels, according to a study conducted in elderly Mexican-Americans.[8]

7. AIR POLLUTION AND TYPE 2 DIABETES MELLITUS

In recent years there has been an interest in air pollution and its possible role in the etiology of diabetes mellitus. Air pollution and diabetes mellitus are critical public health problems around the world. A large number of epidemiological studies have highlighted the adverse effects of air pollution on diabetes and include risk profiles for different exposure durations, types of study design, subgroup populations, and effects of air pollution components. Meta-analyzes on the association between air pollution and diabetes mellitus have focused mainly on studies conducted in high-income countries.[9] In a survey carried out in Switzerland that included 6392 participants whose ages ranged between 29 and 73 years with an estimated exposure of 10 years to particulate matter less than 10 μm in diameter (PM_{10}) and nitrogen

dioxide, it was found that 5.5 % (315 cases) developed diabetes mellitus. Both PM_{10} and nitrogen dioxide particles were associated with the prevalence of diabetes. The association with PM_{10} was marked compared to nitrogen dioxide. Hence, prolonged exposure to contamination is associated with the development of diabetes and the measurement of PM_{10} is suggested as useful markers relevant to diabetes mellitus.[10]

In an investigation carried out in databases where 1878 studies were revised, among which 16 studies with 18 cohorts were included, the incidence of diabetes was significantly associated with an increase in $PM_{2.5}$ and PM_{10} of 10 μg / m^3. The stratified analysis confirmed that $PM_{2.5}$ was significantly associated with the increased incidence of diabetes mellitus in American countries but not in European countries. It seems that both educational level and gender could potentially affect the impacts of PM_{10} and $PM_{2.5}$ on the incidence of diabetes mellitus.[11]

Current accumulated evidence seems to suggest that biomarkers related to diabetes mellitus increase with increasing duration of exposure and the concentration of air pollutants. Chemical constituents of the air pollutant mix can affect diabetes mellitus to varying degrees. Suggested mechanisms by which air pollutants induce diabetes mellitus include increased inflammation, oxidative stress, and endoplasmic reticulum stress.[12]

8. AIR POLLUTION AND HEMOGLOBIN

In a cohort of older adults that included both men and women in the United States, exposures to $PM_{2.5}$ and nitrogen dioxide were significantly associated with the prevalence of diabetes mellitus and increased glycated hemoglobin levels among non-diabetic and diabetic participants. This association suggests that air pollution could be a key risk factor for abnormal glucose metabolism and diabetes in the elderly.[13] In addition to this, in another cohort study in which older adults also participated, it was reported that exposure to polluted air was significantly associated with a higher prevalence of anemia and a decrease in hemoglobin levels.[14]

On the other hand, the association between prenatal and perinatal exposure to fine particles with a diameter less than 2.5 μm ($PM_{2.5}$) and changes in glycated hemoglobin in children between 4 and 7 years of age has also been studied. The findings, although not conclusive, suggest that prenatal and perinatal exposure to $PM_{2.5}$ are associated with changes in glycated hemoglobin, which is an indication of dysregulation of glucose metabolism that may represent a risk factor for the development of diabetes in the childhood or adolescence.[15]

9. ACTIONS OF OZONE AND ENDOGENOUS HYDROGEN PEROXIDE ON ACETONE DEGRADATION IN THE HUMAN BODY

In healthy people, acetone is formed in very small amounts from acetoacetate by the loss of a carboxyl group. Acetoacetate is easily decarboxylated, either spontaneously or by the action of acetoacetate decarboxylase.[16] Acetone levels vary depending on many factors, such as infancy, pregnancy, lactation, physical exercise, dieting, starvation and alcohol consumption.[17, 18] Acetone is also present in a small amount in the blood and urine. Untreated diabetes mellitus leads to overproduction of ketone bodies, with several associated medical problems. In severe ketoacidosis, the increased blood levels of β- hydroxybutyrate and acetoacetate lower the blood pH.[19] Extreme acidosis can lead to coma and in some cases death.[20, 21] In the blood and urine of untreated diabetic patients can reach extraordinary levels (< 3 mg/100 mL normal blood vs.90 mg/100 mL extreme ketosis and ≤125 mg/24 h vs 5 000 mg/24 h.[19] The ratio of glucose / ketone bodies in urine can vary from 5.0 to 6.66 in type 2 diabetic patients with poor metabolic control. Acetone, as volatile substance is excreted, mostly by the kidneys and lungs, but also is metabolized to pyruvate and glucose[22] leading to hyperglycemia or degraded to reactive intermediates (See Part I).

Free radicals are involved as mediators in several biochemical reactions, and they are needed for life.[23] Oxidized halogens, oxidant radicals, and hydrogen peroxide contribute in the destruction of invasive pathogens, induce the release of cytokines and exert influence on some reproductive events.[23] Their overproduction, however, are implicate in the pathogenesis of the most diseases including diabetes mellitus.[23] Levels ≥50 μM hydrogen peroxide are described as cytotoxic to a wide range of living cells, although the lethal doses and the mode of cell death depend on the cell type, physiological condition, length of exposure and the concentration of hydrogen peroxide.[24] It is therefore thought that hydrogen peroxide is very toxic *in vivo* and must be rapidly eliminated. Hydrogen peroxide levels are regulated by the action of antioxidant defense enzymes as catalase, but also by other substances such as ascorbate and glutathione or by exhalation and excretion in urine, [24] under certain conditions might be a valuable biomarker of oxidative stress. Oxidative stress induced complications of diabetes may include stroke, neuropathy, retinopathy and nephropathy.[23, 25]

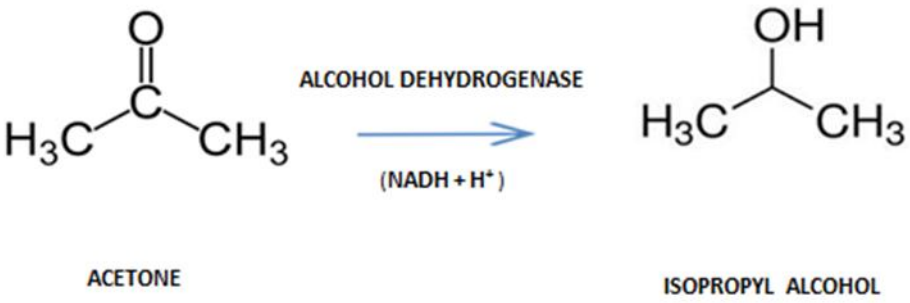

Figure 1: Biotransformation of acetone to isopropyl alcohol in the human body in diabetic ketoacidosis. Reduction of acetone is catalyzed by alcohol dehydrogenase in a reaction dependent of NADH+H$^+$ (an active form of B_3 vitamin).

As shown in Table 1, acetone is degraded by hydrogen peroxide/UV and ozone/UV, yielding similar products, but some of these products have been identified in humans when labeled acetone is administered.[26] In addition to this, isopropyl alcohol, the primary metabolite of acetone degradation (Figure1), by enzymatic metabolism yields similar products (See Note 2, Table 1.). These observations permit to hypothesize that both; acetone and isopropyl alcohol, can be degraded in the body by endogenous hydrogen peroxide or by enzymatic systems contributing on this way to develop diabetes mellitus and other diseases throughout the formation of highly reactive intermediates as methylglyoxal (Figure 2). Methylglyoxal is an important precursor in the formation of advanced glycation end products.[27] The effects of hydrogen peroxide and ozone on acetone and isopropyl alcohol could partly explain the mechanisms by which atmospheric pollutants, such as ozone, contribute to the development of chronic-degenerative diseases in people living in highly polluted urban areas.

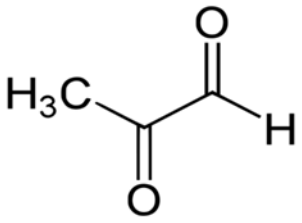

Figure 2: Chemical structure of methylglyoxal, Methylglyoxal is emerging as a new diabetes marker since it plays a significant role in biological processes.[28] Apart from diabetes mellitus, methylglyoxal causes several metabolic irregularities like hypertension, neuropathy, nephropathy, oxidative stress. Methylglyoxal reacts with biomolecules containing aminogroups: proteins, aminophospholipids and nucleic acids.

As a precursor in the formation of advanced glycation end products has been associated with protein dysfunction, glycation of vascular tissues and aging.[28] It is also formed from glucose and fructose metabolism intermediates; glyceraldehyde-3-phosphate and dihydroxyacetone phosphate,[29,30] and from the metabolism of lipids and proteins.[30]

Table 1: Acetone degradation under two physicochemical conditions.

Acetone	**1.1 mM acetone and 15 mM H_2O_2/UV[31, 32]**	**5 mM acetone in 0.05 M phosphate buffer, pH 7.0, Ozone/UV[33]**
Intermediate formed	1. Acetic acid 2. Pyruvic acid 3. Oxalic acid 4. Pyruvic aldehyde 5. Formic acid 6. Glyoxylic acid 7. Hydroxyacetone 8. Formaldehyde ----------	1. Acetic acid 2. Pyruvic acid 3. Oxalic acid ---------- 4. Formic acid 5. Glyoxylic acid ---------- 6. Formaldehyde 7. Methyglyoxal

NOTE 1. When 2-^{14}C-Acetone was administered to humans several compounds among them: 1. Acetic acid. 2. 2-^{14}C-Pyruvic acid. 3. Formic acid. 4. Formaldehyde 5. Methylglyoxal. 6. 2-^{14}C-Acetol (1-Hydroxyacetone). 7. Propylene glycol and 8. Glucose (1, 2, 5, 6-^{14}C) were identified. [34]

NOTE 2. By enzymatic systems involving alcohol dehydrogenase, **i**sopropyl alcohol, primary metabolite of acetone yields: 1. Hydrogen peroxide. 2. Acetone, 3. Acetol, 3. Acetic acid, 4. Formic acid, 5. Propyleneglycol, and 6. Methylglyoxal.[35]

CONCLUSIONS

In conclusion, here is an overview of new concepts related to the clinical importance of acetone. Despite the fact that for several decades it has been insisting with scientific evidence that it is not a waste substance, it is still considered inert and only useful for diagnosing diabetes and ketoacidosis. It will surely soon go from being an inadvertent molecule to being the center of attention of many studies in the basic and clinical areas in order to understand its participation in various metabolic processes, but also to know its participation in the development of several diseases not only diabetes mellitus. It is hypothesized that the role of hydrogen peroxide on acetone which is enhanced by ozone may be a partial explanation of the molecular mechanisms involved in the development of diabetes mellitus and its complications in polluted urban areas.

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