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ACETONE, THE THIRD KETONE BODY. I. PRESENCE IN THE HUMAN BODY IN HEALTH AND DISEASE

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ABSTRACT

Acetone is the simplest of ketones, it is a colorless and flammable liquid, with a somewhat pungent and aromatic smell. Because of its polar character, it is easily mixed with water, ether, methanol, ethanol, and esters. In the industry acetone is mainly used as a solvent for cellulose acetate, nitrocellulose, and acetylene and as a raw material for the synthesis of various organic products such as acetic anhydride, mesityl oxide and methyl isobutyl ketone. Initially it was obtained by distillation from some organic materials or by chemical synthesis. Then it was obtained by fermentation using melase and different microorganisms including *Clostridium acetobutylicum*. It is currently produced from petroleum derivatives. In the human body acetone is produced by lipid metabolism, specifically by decarboxylation of acetoacetate and is exhaled during respiration. Its presence has been controversial, while some authors consider it waste material others consider it a useful marker in the diagnosis of diabetes when its exhalation is excessive. The curiosity to know its effects on the body has led some researchers to inhale its vapors and others to ingest it. Acetone is toxic and the toxicity depends on the time and amount inhaled but also on the physiological conditions of each organism. The use of acetone as a precursor of gluconeogenesis and lipogenesis has been documented with the use of radioisotopes. In recent years, their involvement in glycation of human albumin and hemoglobin, as well as brain aminophospholipids, has been reported and, consequently, their possible association with the development of chronic complications of diabetes mellitus. On the other hand, isopropyl alcohol, its primary metabolite, has been proposed as marker of ketoacidosis. This alcohol is also the precursor of methylglyoxal, a highly reactive dicarbonyl compound with

biomolecules containing amino groups leading to the formation of advanced glycation end products. The last compounds are related not only to the development of diabetes mellitus but also to its complications.

KEYWORDS: Acetone, Diabetes Mellitus, Isopropyl Alcohol, Ketoacidosis, Methylglyoxal, Toxicity, Glycation, Advanced Glycation end Products, Chronic Complications.

1. INTRODUCTION

Triglycerides constitute both 90 % of the dietary lipids and the mayor form of metabolic energy storage in humans. Triglycerides consist of glycerol tri-esters of saturated or unsaturated fatty acids. Like glucose fatty acids are metabolically oxidized to CO_2 and H_2O. In 1904, the German Biochemist Franz Knoop, using chemical labels deduced that the oxidation of the carbon atom β to the carboxyl group is involved in fatty acid breakdown and proposed that this breakdown occurs by a mechanism known as β-oxidation in which the β-carbon atom of the fatty acid is oxidized. It was not until after 1950, following the discovery of coenzyme A (CoA), that the enzymes of fatty acid oxidation were isolated and their reaction mechanisms elucidated.[1]

Acetyl-CoA produced by oxidation of fatty acids in liver mitochondria can be further oxidized via the citric acid cycle. A significant fraction of acetyl-CoA has another fate, however. By a process known as ketogenesis, which occurs primarily in liver mitochondria, acetyl-CoA is converted to acetoacetic acid or β-hydroxybutyric acid. These compounds which together with acetone are somewhat inaccurately referred to as ketone bodies (Figure 1).[1]

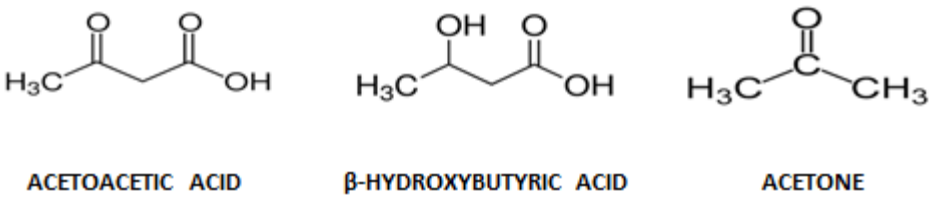

Figure 1. Chemical structure of ketone bodies

β-hydroxybutyrate, which is not, in a technical sense, a ketone according to the International Union of Pure and Applied Chemistry nomenclature.[1] It is considered to be physiologically equivalent to one because it and acetoacetate are readily interconverted in the body.

Acetoacetate (ionized form of acetoacetic acid) or β-hydroxybutyrate serve as important metabolic fuels for many peripheral tissues, particularly heart and skeletal muscle. The human brain under normal circumstances uses only glucose as its energy source but during starvation, ketone bodies become the main source of energy. As it will be described below, acetone is exhaled during respiration and is considered normal in some physiological conditions. Excessive production as occurs in poorly controlled diabetes has been considered a useful auxiliary marker in the diagnosis of diabetes. Today, several studies report adverse effects on the human body. This substance has wide uses in the industry where it is produced by controlled biochemical processes. This article summarizes current knowledge about acetone, third ketone body.

2. ACETONE

2.1. A brief history

Acetone (Figure 1), an organic compound also known as dimethyl ketone, 2-propanone, methyl acetyl and pyroacetic ether was obtained by Libavius in 1595 by dry distillation of lead sugar (lead acetate). In 1805, Trommsdorff reported that by distilling "potassium or sodium acetate" he obtained an intermediate liquid between alcohol and ether. Subsequently, German chemist Justus von Liebig and French chemist Jean Baptiste Dumas, in 1832, determined the exact composition of acetone and its chemical formula. Some years later, in 1852, Alexander William Williamson, an English chemist determined the constitution of ketones and considered acetone as methylacetyl, which was confirmed by reaction of zinc dimethylide with acetyl chloride.[2] In the same year it was agreed/concurred by a French chemist Charles Frederic Gerhardt.[3]

2.2. Physical and chemical properties

Acetone is colorless liquid, its density is 0.7845 g/ml, sweetish in taste, with odor- fruity, pungent, irritating. The physical properties include its melting point of -96.6 ^{0}C and the boiling point of 56.5 ^{0}C. Acetone is miscible with water, benzene, methanol, ethanol, diethyl ether, chloroform. Related to chemical properties of acetone, its molecular weight is 58.08 g/mol. As permanganate and chromic acid, break it down into acetic and formic acids and it breaks down into dioxide of carbon and water.[2,4,5]

2.3. Formation from different sources

Acetone enters the air, water, and soil as a result of natural processes, is formed during animal and human metabolism and produced by human activity. This substance is formed

during oxidation processes, it occurs naturally in plants and trees. There is a small amount of acetone in the pyroleinous acid that results from the dry distillation of the wood. Acetone is also formed from thermal decomposition of coal, acetate, formate and citric acid, and in the dry distillation of sugars or gums with lime. It also results from the dehydrogenation or oxidation of isopropyl alcohol vapor at high temperatures in the presence of catalysts (Figure 2).[2] As it will be discussed below, people breathe out acetone produced from the natural breakdown of body fat.

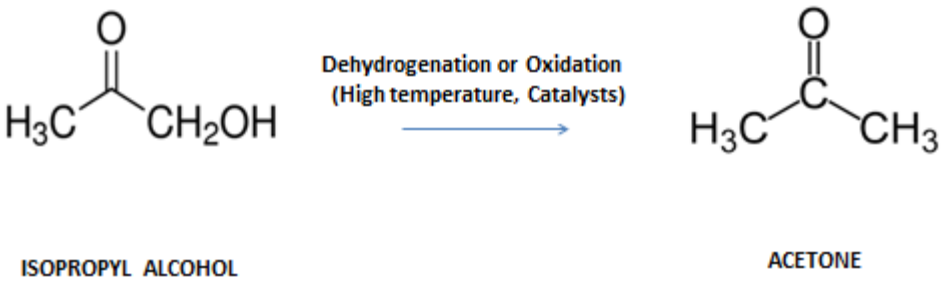

Figure 2. Acetone production from isopropyl alcohol at high temperatures.[2]

2.4. Industrial manufacturing and uses

Until the entry of the United States into World War I, acetone was produced in that country by dry distillation of calcium acetate, which was obtained by neutralizing pyroleinous acid with lime and evaporating the product to dryness.[5] This procedure was suspended in 1925. Subsequently, due to the demand it was produced by fermentation of cornmeal using cultures of *Clostridium acetobutylicum.* With the discovery of new cultures of microorganisms, molasses were used, a procedure that has been used since 1930, but the shortage of molasses led to the implementation of acetone production from propylene extracted from petroleum, from which a quality product is obtained useful in the manufacture of cellulose acetate to make artificial silk, photographic and plastic films, in addition to various industrial uses.

As historical data it is known that in 1940 in the United States approximately 200 000 000 pounds equivalent to 90 718 000 kg of acetone were manufactured and probably no more than 20% of that amount was produced by fermentation. Most of the acetone was used to make acetic anhydride. In 1944, 328 000 000 pounds equivalent to 148 777 520 kg of acetone from isopropyl alcohol were produced and about 25 401 040 kg by fermentation, reaching in1946, 152 403 063 kg of acetone.[2] Today, The United States has the highest production capacity of acetone, nearly 1.70 million tonnes per year, followed by Taiwan and China. The

largest acetone producing company is INEOS Phenol, which owns around 17% of the world's capacity, followed by Mitsui, Sunoco, and shell.[3]

Several derivatives for industrial use are obtained from acetone; Diacetonalcohol (4-hydroxy-4-methyl-2-pentanone), Mesityl oxide (4-methyl-3-pentene-2-one), Methylisobutyl ketone (4-methyl-2-pentanone), Methylisobutylcarbinol (4-methyl-2 -pentanol), 2-Methyl-2,4-pentanediol, Cetena, Isophorone and methyl methacrylate.

3. HEALTH AND SAFETY CONSIDERATIONS

3.1. Observations in industrial workers

Published reports about the harmful effects that acetone produces on industry workers are extremely rare and sometimes inaccurate. The intake of 15 to 20 g per day for several days, Albertoni showed, produces no other disorder than mild drowsiness, but inhalation has serious consequences due to the high volatility of the liquid. Kagan, in personal experiences, could not inhale the concentration of 800 ppm for more than 5 minutes due to severe throat irritation.[6] In general, there is no indication that acetone is harmful to workers who handle it in well-ventilated spaces, ventilation that is necessary to avoid the risk of fire from accumulation of acetone vapors. However, in a very interesting article on hazardous substances and their health effects published by the Agency for Toxic Substances and Disease Registry of the Unites States (ASTDR),[7] is established that the effects of exposure to any hazardous substance depend on the dose, the duration, how the person exposed, personal traits and habits, and whether other chemicals are present. Workers and people exposed to acetone in the lab complained that acetone irritated their noses, throats, lungs, and eyes. Some people feel this irritation at levels of 100 ppm acetone in the air, and more people feel the irritation as the level in air increases. The workers who complained of irritation were exposed to levels of 900 ppm or more. Workers exposed to acetone at 12,000 ppm or higher also complained of headache, lightheadedness, dizziness, unsteadiness, and confusion depending on how long they were exposed (from 2 minutes to 4 hours). Two workers exposed for 4 hours became unconscious.[7] In addition, some people who had casts applied with acetone were exposed to acetone that evaporated into air during and after the casts were applied. These patients became nauseous, vomited blood, and became unconscious.

3.2. Observations in animals

It is not known whether all the effects seen in animals would occur in humans, but it is known that animals briefly exposed to high levels of acetone in the air also had lung irritation

and became unconscious; some died. Exposure at lower levels for short periods also affected their behavior. Pregnant animals that were exposed to high levels of acetone in air had livers that weighed more than usual and had fewer fetuses. The fetuses weighed less than normal and had delayed bone development.[7]

Animals given large amounts of acetone to swallow or drink for short periods had bone marrow hypoplasia (fewer new cells being made), degeneration of kidneys, heavier than normal livers and bigger liver cells, and collapse and listlessness. Male rats that swallowed or drank even small amounts of acetone for long periods had anemia and kidney disease, also had abnormal sperm. Pregnant mice that swallowed acetone had lower body weights and produced fewer newborn mice. More of the newborns of mice that had swallowed acetone died than newborns of mice that were not given acetone.

Acetone is irritating to the skin of animals when it is placed directly on their skin, and it burns their eyes when placed directly in their eyes. One kind of animal (guinea pigs) even developed cataracts in their eyes when acetone was placed on their skin.[7]

4. ACETONE FORMATION IN THE HUMAN BODY

Fatty acids obtained by diet or lipolysis are oxidized in the mitochondrial matrix yielding acetyl CoA, which is subsequently converted to acetoacetic acid and β-hydroxybutyric acid. As shown in Figure 3 and Figure 4, in healthy people, acetone is formed in very small amounts from acetoacetate by the loss of a carboxyl group. Acetone is described as a biologically inert side product.[8] Acetoacetate is easily decarboxylated, either spontaneous or by the action of acetoacetate decarboxylase.[9] Acetoacetate decarboxylase is an enzyme involved in both the ketone body production pathway in humans and other mammals,[9,10] and solventogenesis in bacteria.[11] Several conditions can lead to high amounts of acetone in the human body. Acetone levels vary depending on many factors, such as infancy, pregnancy, lactation, physical exercise, dieting, starvation, alcohol consumption.[7, 12] Acetone is also present in a small amount in the blood and urine. It has been described that these amounts of acetone usually do not cause health problems.

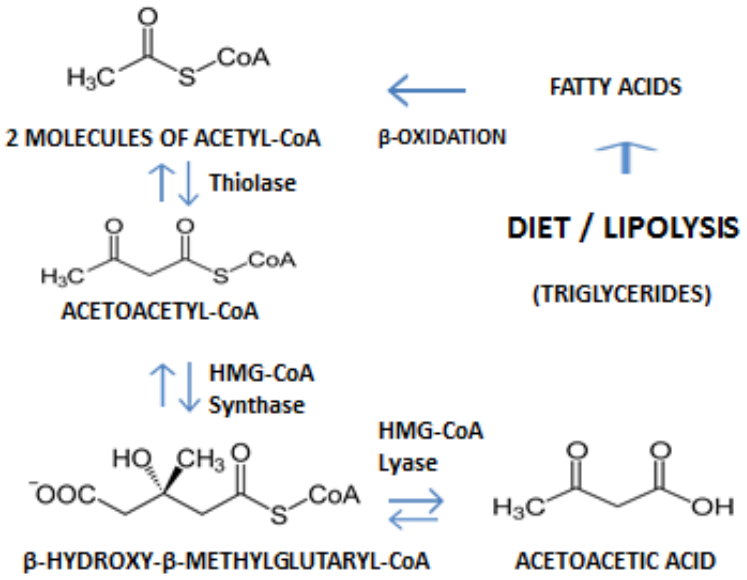

Figure 3: Formation of acetoacetic acid from fatty acids. The oxidation of fatty acids in the mitochondrial matrix by β-oxidation produces acetyl Co-A, which is converted to acetoacetyl-CoA by thiolase. Then acetoacetyl-CoA is converted to β-hydroxy- β-methylglutaryl-CoA (HMG-CoA) by HMG-CoA synthase. Subsequently, acetoacetic acid is formed by the enzyme HMG-CoA lyase from HMG-CoA.

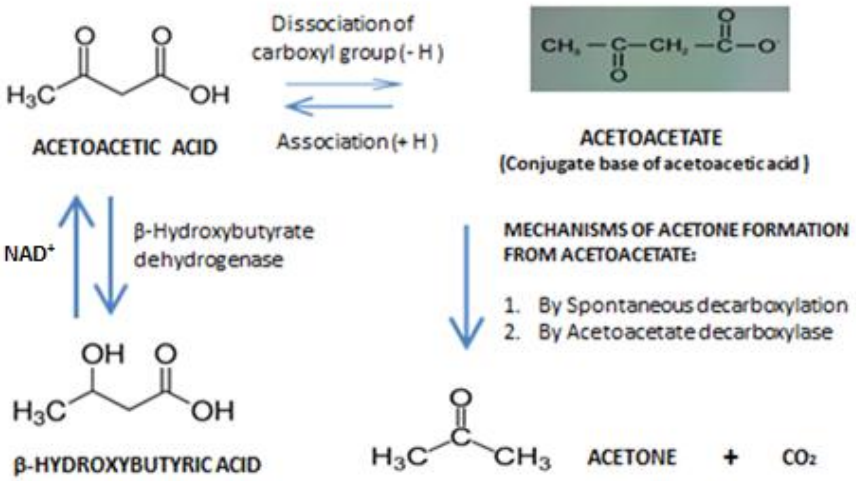

Figure 4. Formation of β-hydroxybutyric acid and acetone from acetoacetic acid. The conversion of β-hydroxybutyric acid to acetoacetic acid is catalyzed by the enzyme β-hydroxybutyrate dehydrogenase that requires of oxidized nicotinamide adenine dinucleotide (NAD^+), the active form of vitamin B_3. Acetone is formed from acetoacetic acid either by spontaneous decarboxylation or by the enzyme acetoacetate decarboxylase.

5. USEFULNESS IN THE DIAGNOSIS OF KETOACIDOSIS AND DIABETES

With the idea that acetone is in a small amount in normal blood and urine and does not cause health problems, it has been considered an inert and waste substance.[8, 12] Due to its volatility it imparts a sweet odor to the breath, which sometimes useful in diagnosing ketoacidosis[12] and diabetes.[8, 13-15] However, individuals with untreated diabetes produce large quantities as a product of decarboxylation of acetoacetate (Figure 4), their blood and urine contain significant amounts of acetone, which is toxic. On the other hand, there are several reports indicating that acetone is used in normal processes to form glucose and fats to produce the energy the body requires.[7]

6. METABOLIC STUDIES IN EXPERIMENTAL MODELS

In healthy cows an elevation of ketone bodies was induced by reduction of feed intake. Acetone concentrations in exhaled breath were measured by gas chromatography combined with mass spectrometry.[16] These values were correlated with concentrations of serum β-hydroxybutyric acid (r = 0.81) and milk acetoacetate + acetone (r = 0.70). It was concluded that the ketotic state of dairy cows can be detected by analysis of exhaled breath, a potential non-invasive method of determining the metabolic state of dairy cows.[16]

To study the metabolic fate of [U-^{14}C]acetone and other labeled metabolites such as $NaH^{14}CO_3$, L-[U-^{14}C]lactate, [2-^{14}C]acetate or D-[U-^{14}C]- plus D-[3-^{3}H]-glucose, these substances were administered *i. v.* to rats starved for 3 days. From the change in the plasma concentration of labeled acetone versus time after the injection, the metabolic clearance rate of acetone was calculated as 2.25 ml/min per kg body weight, and its rate of turnover as 0.74 nmol/min per kg. Some 1.37% of the ^{14}C atoms of circulating glucose originated from plasma acetone, compared with 44% originating from lactate. It was shown that the flux of C atoms from acetone to glucose reached a peak at about 100 min after injection of labeled acetone. It was concluded that acetone is converted into lactate to a degree sufficient to account for the labeling of plasma glucose and is thus a true substrate of glucose synthesis in starved rats.[17]

7. METABOLIC STUDIES IN HUMANS

The metabolism of acetone was early studied in lean and obese humans during starvation ketosis. Acetone concentrations in plasma, urine, and breath; and rates of endogenous production, elimination in breath and urine, and *in vivo* metabolism were determined.[18] When [^{14}C]-acetone was used, radioactivity was found in plasma glucose, lipids, and proteins but was not detected in plasma free fatty acids, acetoacetate and β-hydroxybutyrate. It was

though that if glucose synthesis from acetone is possible in humans, this process could account for 11% of the glucose production rate and 59 % of the acetone production rate in 21-d fasted subjects. During maximum acetonemia, acetone production from acetoacetate could account for 37% of the anticipated acetoacetate production, which implies that a significant fraction of the latter compound does not undergo immediate terminal oxidation.[18]

Later, plasma acetone turnover rates were measured with the primed continuous infusion of 2-[^{14}C]-acetone in patients with moderate to severe diabetic ketoacidosis, turnover rates were directly related to the plasma acetone concentrations. The average acetone turnover rate was 6.45 μmol kg−1 min−1 (533 μmol • 1.73 m−2 min−1), a value twice that obtained in a similar group of diabetic ketoacidotic patients via the single-injection technique of 2-[^{14}C]-acetone administration.[19]

Degradation of urine glucose revealed that ^{14}C from administered 2-[^{14}C]-acetone was principally located in carbons 1 (carbon of aldehyde group), 2, 5, and 6 of the glucose molecule in five of six patients **(**Figure 5). This distribution was similar to that expected from 2-[^{14}C]-pyruvate, suggesting that acetone was converted to glucose through pyruvate.[19] Acetol and 1,2-propanediol (Figure 5), two possible metabolites of acetone, were detected in plasma of the patients.[19] The concentrations of acetol ranged from 0 to 0.48 mM and of 1, 2-propanediol ranged from 0 to 0.53 mM. The concentrations of each metabolite were related to the plasma acetone concentrations.

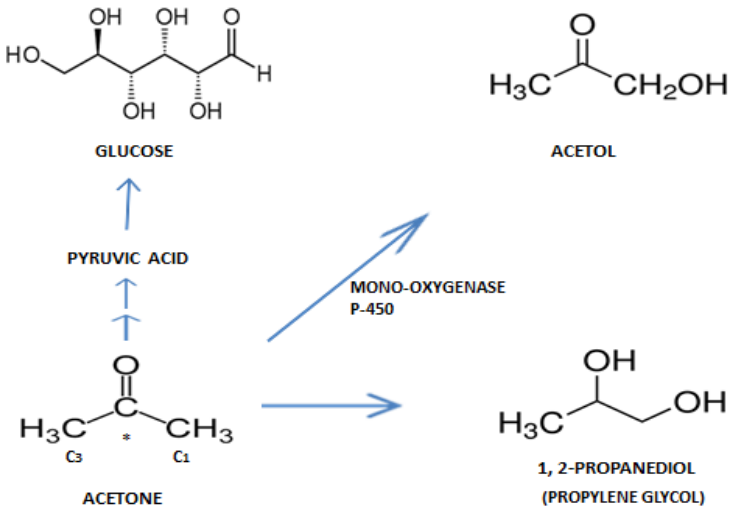

Figure 5: Acetone metabolism in the human body. The use of 2-[^{14}C]-acetone (*) has shown that acetone is converted to glucose through pyruvate formation. Other substances such as acetol (Synonyms: 1-Hydroxyacetone, 1-hydroxy-2-propanone) and

1, 2-propanediol (Synonyms: Propane-1, 2-diol, 1, 2-dihydroxypropane, methyl ethyl glycol, methylethylene glycol, propylene glycerol, propylene glycol) derived from acetone have been detected in human plasma.[19]

Further in 1999, the metabolic pathway for acetone metabolism was proposed, acetone was no longer considered a waste product of metabolism and a model to explain its role in acetonemia was stated.[20] In that model it was suggested that the events that occur in acetonemia follow an ordered sequence that implies first its participation in the regulation of pH and second, its metabolism in the liver contributing to the glucostatic function providing C3 fragments to peripheral tissues as additional fuel.[20]

8. ACETONE IN SEVERE KETOACIDOSIS

Diabetic ketoacidosis consists of the biochemical triad of hyperglycemia, ketonemia and metabolic acidosis, resulting from absolute or relative insulin deficiency in the presence of an increase in counterregulatory hormones.[21] It is classified in three categories: a). Mild ((Plasma glucose (mg/dL): >250 (>13.9 mM), arterial pH: 7.25–7.30, serum bicarbonate: 15–18 mEq/L), b). Moderate ((Plasma glucose (mg/dL): >250, arterial pH: 7.00- < 7.24, serum bicarbonate: 10- <15 mEq/L) and c) Severe (Plasma glucose (mg/dL): >250), arterial pH: <7.00, serum bicarbonate: <10 mEq/L).[21]

Ketone bodies are found in blood of healthy individuals, neonates or pregnant women, the liver is capable of producing 185 g of ketone bodies per day.[13] Acetoacetate and β - hydroxybutyrate provide cells with acetyl-CoA that is subsequently oxidized for energy in the citric acid cycle. After eating food, the ratio of β-hydroxybutyrate / acetoacetate is approximately 1.0 but can be increased to 6 in prolonged fasting and exercise.[22] Large quantities of ketone bodies can be found in the blood of individuals with alcoholic ketoacidosis. In some pathophysiological conditions such as diabetic ketoacidosis, circulating levels of ketone bodies above 25 mM can be achieved, this occurs more frequently in type 1 diabetic patients[23] and less common in type 2 diabetics. High levels of acetone have been demonstrated in the blood of diabetics in ketoacidosis. The plasma-acetone ranged from 2.5 to 12.9 mM, levels considerably greater than those for blood-acetoacetate measured at the same time have been reported.[24] plasma-acetone remained elevated for periods of up to 42 hours, long after blood-glucose, acetoacetate, and β-hydroxybutyrate levels had returned to normal.

Untreated diabetes mellitus leads to overproduction of ketone bodies, with several associated medical problems. A single episode of moderate/severe diabetic ketoacidosis in young children at diagnosis has been associated with lower cognitive scores and altered brain growth.[25] In severe ketoacidosis, the increased blood levels of β- hydroxybutyrate and acetoacetate lower the blood pH (Figure 6).[26] Ketone bodies have been shown to affect vascular integrity and permeability and contribute to edema formation.[21,27] Extreme acidosis can lead to coma and in some cases death.[28,29] Ketone bodies are also filtered in large quantities by the kidneys, and the fraction that is not re-absorbed is excreted in the urine. 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.[26] 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 unchanged, mostly by the kidneys and lungs (breath), but also is metabolized to pyruvate and glucose[30] leading to hyperglycemia.

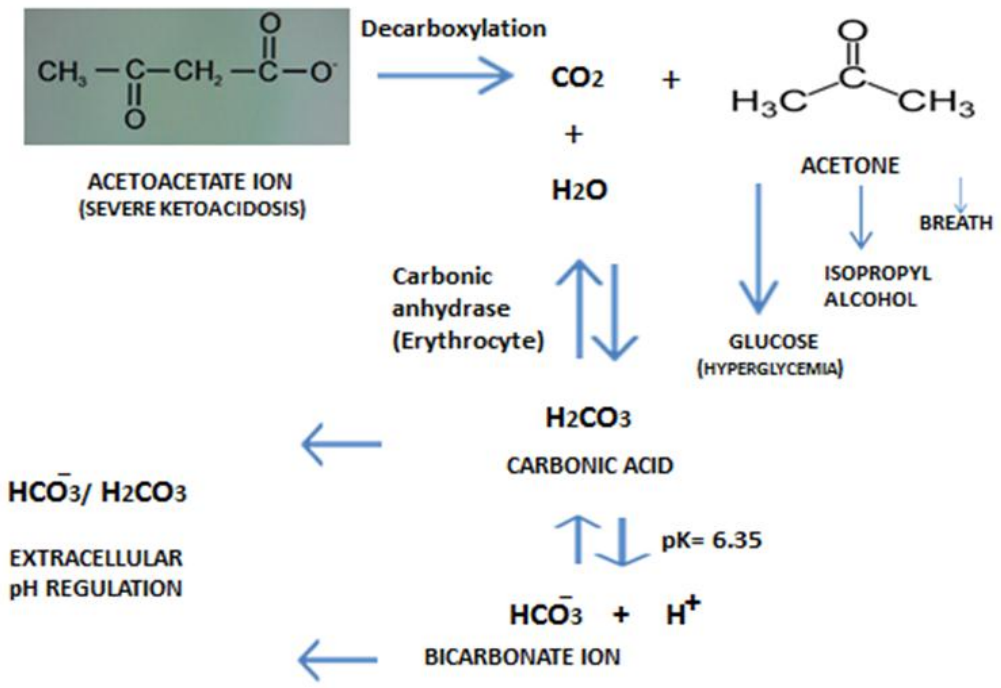

Figure 6. Under conditions of severe ketoacidosis, acetoacetate is decarboxylated producing CO_2 and acetone. CO_2 is hydrated by carbonic anhydrase to form carbonic acid that dissociates producing the bicarbonate ion. This acid-base pair contributes to the regulation of extracellular pH. Acetone is converted to glucose in an attempt to maintain homeostasis but an excess contributes to hyperglycemia development. Since

acetone is produced in high amounts, some is eliminated by respiration but is also transformed to isopropyl alcohol. Both acetone and isopropyl alcohol formed in excessive amounts are toxic to the body, contributing to the development of chronic complications of diabetes mellitus.

9. BIOTRANSFORMATION OF ACETONE TO ISOPROPYL ALCOHOL IN THE HUMAN BODY

When glucose is unavailable as an energy source, as in uncontrolled diabetes, fatty acid oxidation is used to provide acetyl-coenzyme A for energy production. This oxidation generates reduced nicotinamide adenine dinucleotide ($NADH+H^+$), that can in turn reduce acetone to isopropyl alcohol (also known as: Isopropanol, 2-propanol, propan-2-ol). The reaction is catalyzed by hepatic alcohol dehydrogenase **(**Figure 7). The oxidized product of $NADH+H^+$, NAD^+, can then be reused for fatty acid oxidation, leading to further ketone body and $NADH+H^+$, production. Therefore, a high $NADH+H^+$ /NAD^+ (redox) ratio favor the production of isopropyl alcohol from acetone.[30, 31] Disease states known to have these increased redox states include diabetes mellitus and chronic alcoholism.[31] The metabolism is shifted toward the production of isopropyl alcohol from acetone in those patients with extremely high levels of acetone from severe hyperglycemia as occurred in two patients with severe ketoacidosis. In the first case, acetone (45 mg/100 ml) and isopropyl alcohol (17 mg/100 ml) were found.[32] In the second case, levels of glucose, acetone and isopropyl alcohol were: Glucose 2090 mg/100 ml, acetone 97 mg/100 ml (blood) and isopropyl alcohol 5 mg/100 ml (blood), respectively.[33]

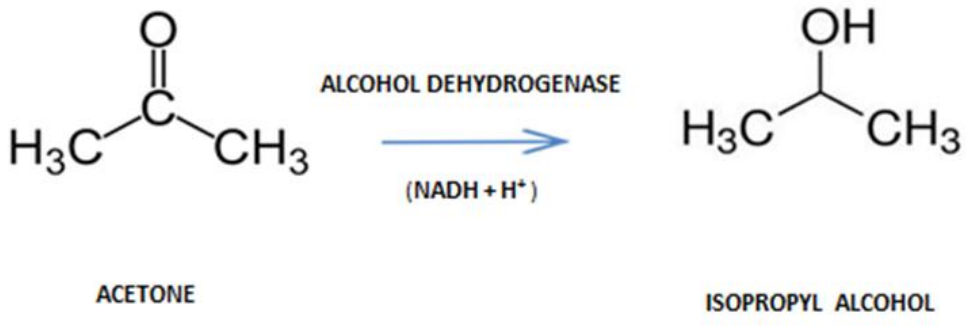

Figure 7. Transformation of acetone to isopropyl alcohol in the human body in diabetic ketoacidosis. Reduction of acetone is catalyzed by alcohol dehydrogenase dependent of $NADH+H^+$.

In type 1 diabetic patient with hyperglycemia and acetonemia not exposed to isopropyl alcohol, a ratio of isopropyl alcohol/acetone between 0.10 and 0.47 was reported, although in one case the proportion was 5.12 with a glucose concentration of 221 mg/100 ml.[34] In type 2 diabetics concentrations of exhaled isopropyl alcohol were significantly higher than the controls and was proposed that endogenously produced isopropyl alcohol can be a valuable biomarker for noninvasive diabetes diagnosis in breathomics analysis.[35] A similar pattern of isopropyl alcohol production was observed in healthy volunteers who were subjected to a ketogenic diet.[35]

10. POSTMORTEM DETERMINATION OF ACETONE AND ISOPROPYL ALCOHOL IN FLUIDS AND TISSUES AS MARKERS OF KETOACIDOSIS

Although since 1950 the finding of considerable amounts of isopropyl alcohol in the blood, milk and rumen of cows suffering from acetonemia has been reported and it was speculated that isopropyl alcohol could be a precursor or a metabolic product of acetone,[36] its presence in humans became known after more than three decades, when it was reported that both isopropyl alcohol and acetone were detected in autopsy blood samples of individuals not previously exposed to these compounds. Since some of these individuals had a history of diabetes mellitus, it was suggested that in these cases, conversion of acetone to isopropyl alcohol might be a metabolic pathway for its production, which was confirmed by experiments carried out in rats,[30] where it was also observed that the formation of isopropyl alcohol from acetone differs between diabetic rats and normal rats.

Later, the concentration of isopropyl alcohol was determined in the body fluids of diabetic individuals who died suddenly and whose death was associated with ketosis. Thus, in femoral blood, the concentration of isopropyl alcohol reported by different authors is in the range of 0.06 to 0.09 mg/100 ml,[37] and from 2.0 to 9.5 mg/100 ml.[38] In urine and vitreous humor the reported concentrations vary from 2.2 to 5.1 mg/100 ml and from 1.7 to 4.9 mg/100 ml, respectively.[38]

Other authors in a retrospective study analyzed 260 deaths in which concentrations of acetone and isopropyl alcohol were determined. Isopropyl alcohol was detected in 77% of ketoacidosis cases with quantifiable concentrations averaging 15.1 ± 13.0 mg/100 ml.[39] Similar concentrations of both substances in blood and vitreous humor had been reported in another retrospective study.[40] The results demonstrated the frequency of detecting isopropyl alcohol in ketoacidosis when there was no evidence of its ingestion. In addition to this, the

ability to produce isopropyl alcohol in various tissues of unexposed decedents was investigated and it was found that isopropyl alcohol was produced by reduction of acetone to pH 7.3 in blood, liver, brain and kidney at concentrations that ranged from 1 - 29, 7 - 59, 2 - 12, 6 - 26 mg / 100 g, respectively.[41] The endogenous formation of isopropyl alcohol has also been determined in lung homogenates.[42] Isopropyl alcohol is currently considered a marker of ketoacidosis in forensic investigations and a product of acetone metabolism in clinical conditions presenting increased ketone body levels.[38, 43]

11. INTOXICATION BY EXOGENOUS ACETONE AND ITS MEDICAL MANAGEMENT

Acetone can be absorbed by inhalation, through the skin and ingestion. The syndrome of acetone intoxication presents as generalized central nervous system/respiratory depression, drowsiness, weakness, nausea, headache, ketosis and hyperglycemia. Elimination of acetone is slow, haemodialysis to enhance elimination may be indicated in severe poisoning.[44] Due to the availability of acetone a variety of intoxication cases have been reported including pediatric patients and adult subjects. In 1988 a case of 30-month-old patient with severe acetone intoxication secondary to fingernail polish remover ingestion was informed and the need to include acetone ingestion in the differential diagnosis of apparent diabetic ketoacidosis was alerted.[45]

When acute intoxication is treated immediately and the elimination of acetone is achieved, subsequent organ damage is avoided. Such is the case of a man who was found unconscious, having swallowed 800 ml of pure acetone (an amount ten times the lethal dose). The serum acetone concentration was 200 mg/100 ml, that in urine 230 mg/100 ml.[46] He was carefully hyperventilated, haemofiltration was performed over 16 hours and forced diuresis with high fluid intake was undertaken. His condition improved after 14 hours. Measurements of acetone in blood and urine indicated its elimination with a half-life of 11 hours.[46] However, lesions of the parenchymal organs were found in four individuals; two males and two females with acute acetone intoxication. In all patients (one of them inhaled acetone vapors and the rest swallowed) hepatic lesion was present with the corresponding clinical manifestations and changes in the laboratory liver indices. In two of the intoxicated, renal lesion was also found, manifested in a milder degree. A timely treatment with hepato- and nephroprotective drugs in large doses could be applied: glucocorticoids, glucose and levulose solutions, B complex vitamins (B_1, B_2, B_{12}), vitamin C and calcium gluconate.[47] Acetone may cause parkinsonism

by damaging the basal ganglia. In 2003 the case of a woman whose parkinsonian features developed after accidental acetone ingestion was reported.[48] She had rigidity, bradykinesia, gait disturbance and her speech was sluggish. After treatment with levodopa, her neurological symptoms improved.

12. EXOGENOUS ISOPROPYL ALCOHOL AND ITS CONVERSION TO ACETONE AND GLUCOSE

Isopropyl alcohol is found in a wide variety of commercial products including solvents, inks, antifreezes, cleaners, disinfectants, hand sanitizer, cosmetics, and pharmaceuticals.[49] It is a clear, colorless liquid with a fruity odor and a mild bitter taste, completely soluble in water. It is readily available to the public at concentrations of 70 % as rubbing alcohol and 99 % for industrial or laboratory use. Isopropyl alcohol causes rapid intoxication, so people sometimes drink it to get drunk. Others use it to attempt suicide,[49] but poisoning can also occur in children since they often drink products that they find at home.[49, 50] Isopropyl alcohol is rapidly absorbed following ingestion with peak plasma concentrations occurring within 30 min. It can also be absorbed following inhalation or dermal exposure as it happened with a baby who accidentally inhaled isopropyl alcohol vapors for an estimated time of 2 hours.[51] When more isopropyl alcohol is ingested than the body can metabolize, which is equivalent to 200 ml for an adult, poisoning can occur. In this condition the liver is no longer able to manage the amount of isopropyl alcohol in the body. Several symptoms may appear immediately or may take a few hours to become noticeable. Isopropyl alcohol poisoning usually causes: Stomach pain, confusion, dizziness, slowed breathing. In severe cases, it can lead to a coma.[50] Isopropyl alcohol is a sedative-hypnotic agent whose toxicity closely resembles that of ethanol, but is more potent at comparable concentrations.[52]

It is described that the body can handle small amounts of isopropyl alcohol. In fact, the kidneys remove approximately 20 to 50 percent of isopropyl alcohol from the body. The rest is broken down into acetone by alcohol dehydrogenase. Then, acetone is exhaled in breath or filtered by the kidneys, but acetone can also be converted to glucose causing hyperglycemia (Figure 8).

In 1981 two cases of acute overdose with isopropyl alcohol that required medical intervention were reported.[53] In the first case, a thirty-eight year old male who admitted drinking one-fourth of a large bottle of rubbing alcohol, the concentration of isopropyl alcohol at diagnosis was 0.17 g / 100 ml of blood, the lethal concentration being 0.15 g / 100 ml and above. He

had a history of heavy consumption of ethyl alcohol. The second case, a female twenty-six year old who drunk a half pint of rubbing alcohol, the concentration of isopropyl alcohol at diagnosis was 0.10 g / 100 ml of blood. She had a past history of consumption of up to one pint of vodka per day, and had been admitted previously for an attempted suicidal drug overdose. Both patients were treated with intravenous fluids. The metabolism of the isopropyl alcohol proceeded in both patients in a relatively rapid manner within twelve hours in each subject (Blood half-lives of 155 and 187 minutes, respectively), acetone, formed from isopropyl alcohol remained high in both subjects. In the second case, it was possible to measure it until for up to 37 hours, but it was calculated that for its total elimination an approximate time of 75 hours was required.[53]

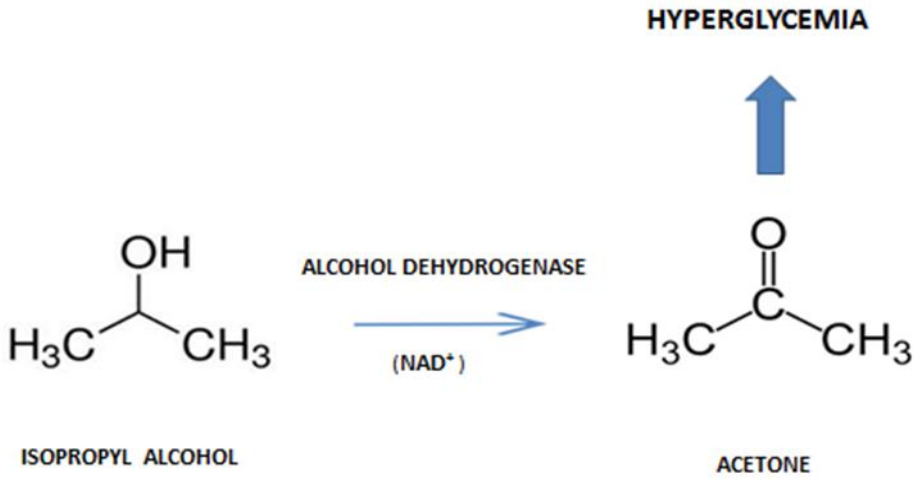

Figure 8. The conversion of exogenous isopropyl alcohol leads to hyperglycemia through the formation of acetone in animals and humans. Oxidation of isopropyl alcohol to acetone is catalyzed by alcohol dehydrogenase dependent of NAD^+.

So the toxic effects attributed to isopropyl alcohol could be due in part to the presence of acetone which is formed from isopropyl alcohol.[53] Previous reports indicate that the elimination half-life of isopropyl alcohol is between 2.5 and 8.0 h, whereas elimination of acetone is slower with a half-life following isopropyl alcohol ingestion of between 7.7 and 27 h.[50]

In another report,[54] a comatose and hypotensive patient was successfully treated with hemodialysis after ingesting 480 ml of isopropyl alcohol. Removal of isopropyl alcohol and acetone were measured in urine, blood, and dialysate. Approximately 19 g of isopropyl

alcohol and 7 g of acetone were removed per hour. Mean dialysis times for isopropyl alcohol and acetone were 137 and 165 ml/min, respectively. Isopropyl alcohol removal was faster than acetone.

Recently, the case of a 33-year-old man found dead with evidence of having consumed pure isopropyl alcohol was reported.[55] The concentrations of isopropyl alcohol and acetone in various body fluids were: 46.4, 26.0, 46.5 and 99.1 mg / 100 ml and 156.0, 234.0, 304.0 and 136.0 mg / 100 ml of blood, vitreous humor, urine and bile, respectively. Although the authors report that the isopropyl alcohol absolute concentrations and isopropyl alcohol/acetone ratios appear inferior to those usually reported in the literature in isopropyl alcohol poisoning cases, these results confirm the conversion of isopropyl alcohol to acetone in the body. However, there are reports informing that isopropyl alcohol is also metabolized to products of intermediary metabolism, among them methylglyoxal.[50]

13. ACETONE AND THE DEVELOPMENT OF CHRONIC COMPLICATIONS IN DIABETES MELLITUS

Glycation or the Maillard reaction is a non-enzymatic glycosylation that occurs when molecules containing amino groups are exposed to elevated concentrations of carbohydrates to form unstable Schiff bases that can then undergo the Amadori rearrangement to form irreversible advanced glycation end products (AGEs**).**[56] In chronic diseases including diabetes mellitus, proteins, aminophospholipds or nucleic acid modifications by glycation are involved. However, the formation of AGEs is not restricted only to the reaction of carbohydrates with the amino groups of biomolecules, so that any molecule that contains a carbonyl group can react with amino compounds.

The glycation of hemoglobin by acetone and β-hydroxybutyrate and brain aminophospholipids by acetoacetate in the absence of carbohydrates has been demonstrated in our laboratory. In an effort to attenuate glycation by ketone bodies, several substances with antiglycating properties have been tested by our group. Among them, glycine, glycylglycine, aminoguanidine, L-arginine, polyamines and urea**.**[57, 58] In other studies using acetone we have demonstrated that the integrity of human erythrocyte is affected by acetone and that the haemoglobin is glycated by this ketone body (see the article, Part 2) contributing to the chronic diseases development.

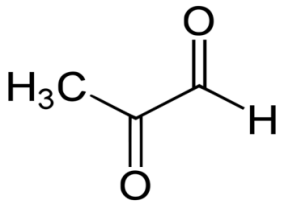

Figure 9: Chemical structure of methylglyoxal.

Methylglyoxal (Figure 9), a dicarbonyl compound highly reactive with molecules containing amino groups is originated from glucose and fructose metabolism intermediates; glyceraldehyde-3-phosphate and dihydroxyacetone phosphate,[59, 60] and from the metabolism of lipids and proteins,[60] but it can also be formed from acetone and isopropyl alcohol,[50, 61] both substances derived from acetoacetate and β-hydroxybutyrate (Figure 10). It is a precursor of AGEs, and it has been implicated in classical diabetic complications such as retinopathy, nephropathy, and neuropathy. Recently, it has also been associated with cardiovascular diseases and central nervous system disorders such as cerebrovascular diseases and dementia.[62] Its participation in insulin resistance and beta-cell dysfunction, contributing to the early development of type 2 diabetes, has also been suggested.[62] Methylglyoxal is emerging as a new diabetes marker since it plays a significant role in biological processes.[63] Apart from diabetes mellitus, methylglyoxal causes several metabolic irregularities like hypertension, neuropathy, nephropathy, oxidative stress. As a precursor in the formation of AGEs has been associated with protein dysfunction, glycation of vascular tissues and aging (Figure 10).[63] In normal situations, cells are protected against methylglyoxal toxicity by different mechanisms and in particular the glyoxalase system, which represents the most important pathway for the detoxification of methylglyoxal.[60]

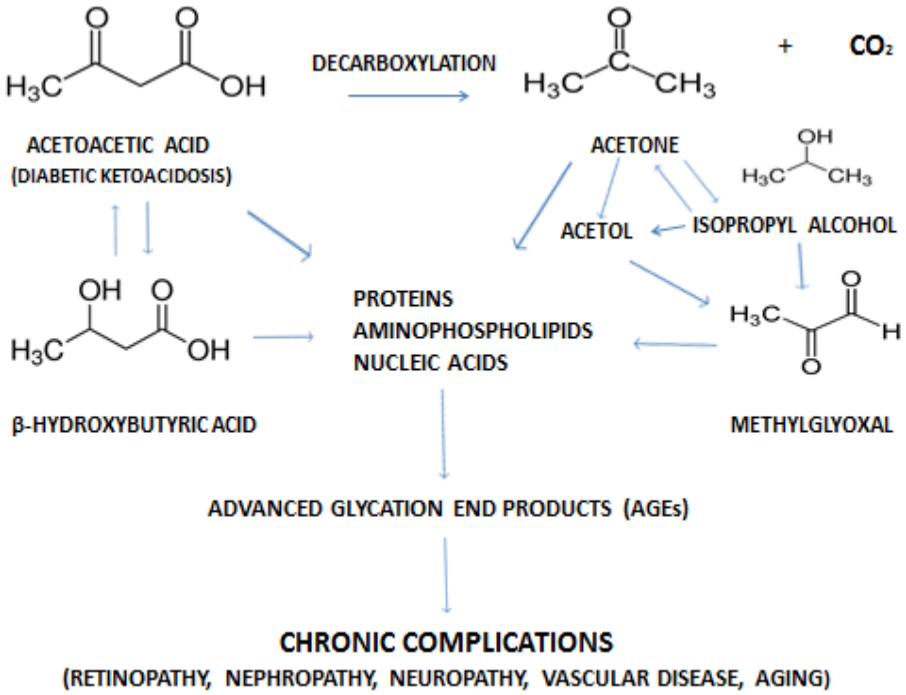

Figure 10. Acetone, methylglyoxal, and its precursors β-hydroxybutyrate and acetoacetate react with biomolecules containing amino groups leading to the formation of advanced glycation end products (AGEs). AGEs are related to the development of chronic complications of diabetes mellitus and related diseases.

14. THE DEGRADATION OF ACETONE AND ISOPROPYL ALCOHOL UNDER DIFFERENT PHYSICOCHEMICAL CONDITIONS PRODUCES SIMILAR INTERMEDIARIES.

Several studies have been carried out on the degradation of both acetone and isopropyl alcohol. In the first case due to the presence of acetone in contaminated waters and in the second case to study the effect of temperature on the decomposition of isopropyl alcohol and the formation of H_2O_2.

14.1. Acetone

Acetone was treated with H_2O_2 / UV light until its complete mineralization.[64, 65] The main degradation products formed when 1.1 mM acetone and 15 mM H_2O_2 aqueous solution was irradiated were: Acetic, pyruvic, and oxalic acids and pyruvic aldehyde, identified as major products, whereas formic and glyoxylic acids, hydroxyacetone, and formaldehyde were considered as minor products (Table 1).[65] This information allowed to integrate a complete scheme of the reactions that occur by the treatment of acetone with H_2O_2 / UV.[65] When 5 mM acetone in 0.05 M phosphate buffer, pH 7.0, was exposed to ozone (4 mg / 200 ml gas /

min) and UV, acetic, oxalic, glyoxylic and pyruvic acids, methylglyoxal and formaldehyde were identified (Table 1).[66]

14.2. Isopropyl alcohol

The oxidation of isopropyl alcohol has been studied at high temperatures (350 - 450 ^{o}C).[67] During the initial stages of the reaction, H_2O_2 and acetone are formed in a linear chain cycle, although there is evidence that a small part of the isopropyl alcohol reacts in a different way, leading to the formation of acetaldehyde and formaldehyde. The reaction subsequently becomes autocatalytic in nature, and a complexity of C1 and C2 products is formed.[67] In the human body, isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone (Figure 8), but other intermediates such as acetol and methylglyoxal, propylene glycol, acetate, and formate with conversion of these metabolites to glucose and other products of intermediary metabolism can be formed (Table 2).[50]

Table 1: Acetone degradation under physiological and physicochemical conditions.

Acetone	**1.1 mM acetone and 15 mM H_2O_2/UV[64,65]**	**5 mM acetone in 0.05 M phosphate buffer, pH 7.0, Ozone/UV[66]**	**The human body 2-^{14}C-Acetone[19]**
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	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 8.Glucose (1, 2, 5, 6-^{14}C).

Table 2: Isopropyl alcohol oxidation.

Condition	**Gaseous Oxidation (350 - 450 ^{o}C) [67]**	**The human body [50] (By alcohol dehydrogenase and other enzymatic systems)**
Intermediate formed	1. H_2O_2 2. Acetone 3. Acetaldehyde 4. Formaldehyde	1. H_2O_2 2. Acetone 3. Acetol 4. Acetate 5. Formate 6. Methylglyoxal, 7. Propyleneglycol

15. POSSIBLE EFFECT OF ENDOGENOUS H_2O_2 ON ACETONE AND ISOPROPYL ALCOHOL DEGRADATION IN THE HUMAN BODY

Free radicals are involved as mediators in several biochemical reactions, and they are needed for life.[68] They are formed by enzymatic systems; the oxidative, from $NADP^+/NADPH+H^+$, the myeloperoxidase pathway and by degradation of purine nucleotide and deoxynucleotide to xanthine, which is converted to uric acid by xanthine oxidase, an oxidative reaction where H_2O_2 is released.[69]

The most important source of free radicals production is the respiratory burst during the activation of aerobic cells. Oxidized halogens, oxidant radicals, and H_2O_2 contribute in the destruction of invasive pathogens, induce the release of cytokines and exert influence on some reproductive events.[68] Their overproduction, however, are implicate in the pathogenesis of the most diseases including diabetes mellitus.[68] H_2O_2 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, under certain conditions might be a valuable biomarker of oxidative stress.[70] Oxidative stress induced complications of diabetes may include stroke, neuropathy, retinopathy and nephropathy.[68,71]

As described above, acetone is degraded by H_2O_2/UV and ozone/UV, yielding similar products, but some of these products are identified in humans when labeled acetone is used (Figure 5). On the other hand, isopropyl alcohol subjected to high temperature or by enzymatic metabolism yields similar products. These observations permit to hypothesize that acetone or its primary metabolite, isopropyl alcohol, can be degraded in the body contributing on this way to develop diabetes mellitus and neurodegenative diseases throughout the formation of highly reactive intermediates as formaldehyde and methylglyoxal. Apart of this, in the search for a rapid test to diagnose ketoacidosis, urinary β-hydroxybutyric acid has been shown to be oxidized by H_2O_2[72] and although it was not to clinically relevant levels, these observations could have clinical implications in development of diseases.

16. CONCLUSIONS

In conclusion, even today acetone is considered in the clinical environment as a negligible waste substance, or in any case as a useful marker in the diagnosis of diabetes mellitus and ketoacidosis. However, for more than two decades it has been demonstrated based on metabolic studies and the use of radioisotopes that it is not a waste product and that it has important physiological and clinical implications.[20]

It is currently known that its formation represents a mechanism for regulating the concentration of acetoacetate and consequently the blood pH, as well as being a precursor in the synthesis of glucose in critical conditions to generate energy that the body requires. Recent studies show that its excessive production leads to the formation of isopropyl alcohol and that both substances are involved in the development of various diseases, including diabetes mellitus.

Undoubtedly, several concepts need to be reviewed, among them, the effect of prolonged fasting and the consequence of ketogenic diets that, although they are medically controlled, [73] methylglyoxal formed by degradation of acetone can lead to the formation of AGEs over periods of time relatively short, as occurs with glucose, where it has been reported that short periods of hyperglycemia may be sufficient to increase the concentrations of alpha-oxoaldehydes *in vivo* and consequently lead to the formation of AGEs.[61]

Recently was reported that patients suffering from Parkinson disease fed with a ketogenic diet showed several adverse effects compared with those who received low fat diet. The most common adverse effect was exacerbated tremor and/or rigidity, which occurred in 50 % of patients in weeks 1 to 4 and 29 % in weeks 5 to 8.[74] Authors speculated that the abrupt increase in fat intake temporarily augmented dopamine depletion and/or oxidative stress in the substantia nigra. These observations are in accordance with those reported previously in cases of intoxication by exogenous acetone which may cause parkinsonism by damaging the basal ganglia.[48]

Finally, the discovery of the formation of several highly reactive intermediates by the effect of H_2O_2, ultraviolet light, ozone, heat and enzymatic activity, opens a new panorama in the investigation of the role that acetone plays in the human body, particularly in disease conditions.[61]

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