"HOW DOES PROLONGED STARVATION INFLUENCE FATAL KETOACIDOSIS IN DIABETIC PATIENTS? INSIGHTS FROM AUTOPSY CASE STUDY"

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ABSTRACT

Background: Voluntary starvation is a rare cause of death. Full understanding of how comorbidities interact is crucial for characterizing the pathological cascades of death. In the present case, we discuss and illustrate the intertwined relationship between prolonged starvation and diabetes mellitus (DM), with a focus on the psychological aspects and the complexity of food strikes as a method of suicide. **Case Presentation**: A 49-year-old male voluntarily withheld food but consumed juices for almost two years. He was admitted to the hospital due to altered consciousness, blood acidosis, and died within 48 hours from the insulin treatment initiation. Postmortem vitreous analysis detected diabetic ketoacidosis (DKA) with glucose level of 325 mg/dl which surpassed the fatal level of > 234 mg/dl. Prolonged fasting was accompanied by insulin deficiency and insulin resistance which was not reversed by treatment at hospital. **Conclusion:** Lack of other pathological or toxicological findings suggests that the fatal DKA was the cause of death. Hence, starvation condition might have aggravated the diabetic state and the insulin resistance. The cardiac arrest was consistent with arrhythmia secondary to profound electrolytes disturbance associated with severe DKA non-responsive to insulin therapy with short duration from presentation to death.

Keywords*:* Forensic pathology, starvation deaths, intentional dieting, diabetes mellitus, starvation-induced insulin resistance, hyperglycemic ketoacidosis acidosis.

INTRODUCTION

Starvation is defined as the prolonged, irregular, or continuous lack of food and/or fluid intake. Acute starvation refers to total fasting, while chronic starvation is identified by malnutrition **(Madea, Ortmann and Doberentz, 2016).** From a medicolegal perspective, the manner of death may be classified as homicide, suicide, or accidental, depending on the specific circumstances, such as criminal neglect of dependent individuals (**Fieguth *et al.,* 2002)**, hunger strikes (voluntary food withholding for political reasons) **(García-Guerrero *et al.,* 2015)**, and accidental starvation during events like famines and wars (**Garland and Irvine, 2022)**. Both acute and chronic pathological conditions, including systemic and mental illnesses like malignancies, tuberculosis, drug addiction, dementia, and eating disorders, can also be implicated **(Madea, Ortmann and Doberentz, 2016; Garland and Irvine, 2022).** Diabetes mellitus (DM) shares the nutritional deprivation seen in chronic starvation, leading to significant metabolic and pathological changes in various organs **(Agarwal *et al.,* 2016)**. Type I DM is associated with eating disorders, while Type II DM is closely linked to obesity. For forensic pathologists, DM is often viewed as a contributing factor in deaths related to cardiovascular disease due to its impact on myocardial glucose and free fatty acid (FFA) metabolism, the early and severe development of atherosclerosis, and diabetic ketoacidosis (DKA) **(Zinman *et al.,* 2015)**. DKA is a serious complication with a mortality rate of 1.2% to 5% **(Wild *et al.,* 2004**). During prolonged starvation or untreated DM, glycogen stores in the liver and muscles are depleted. As a result, fat stores are mobilized through lipolysis, increasing blood FFA levels. The liver then converts these FFAs into ketone bodies (KB) for energy production **(Altun *et al.,* 2004; Brocchi *et al.,* 2022)**. In DKA, the production of KBs surpasses the kidneys' ability to compensate, leading to severe metabolic acidosis, which can be fatal **(Dhatariya and Vellanki, 2017).** The combined effects of prolonged starvation and DM on the kidneys exacerbate renal dysfunction due to protein deficiency **(Yeow *et al.,* 2016)**. A forensic

autopsy is crucial for determining the primary cause of death in starvation cases, ruling out other comorbidities, and establishing the duration, manner, and ultimate cause of death **(Garland and Irvine, 2022)**. Pathophysiological changes, particularly those related to electrolyte imbalances, can be difficult to detect as the postmortem interval increases. Therefore, postmortem biochemical analyses, alongside classical autopsy, are essential **(Zilg *et al.*, 2009)**. The purpose of this case study is to illustrate the complex relationship between prolonged voluntary starvation and type II diabetes mellitus (DM), with a focus on the psychological aspects and the complexity of food strikes as a method of suicide."

CASE REPORT

A 49-year-old was admitted to the intensive care unit in the hospital due to deteriorated consciousness and hypotension (65/40 mmHg). Laboratory work up revealed leukocytosis, initial hyperglycemia of 634 mg/dl with and severe blood acidosis (pH = 6.98). The medical file of the deceased indicated that he was initially obese (body weight =130 kg and body height = 190 cm) and suffered from type II DM. He was on prolonged voluntary starvation but drinking fluids and juices for almost two years. Insulin was administered for less than 48 hours before he deceased, two hours after his last dose due to cardiac arrest despite the cardiopulmonary resuscitation. Medico-legal autopsy was performed in the next day. This case report was reviewed and approved by the Supreme Council of University Hospitals, Central Scientific Research Ethics Committee (NO. 039).

AUTOPSY FINDINGS

EXTERNAL EXAMINATION

The body was at the stage of rigor mortis, body weight was 80 kg, BMI was 22.2 kg/m2 (within the normal range). He lost ~50 kg of his initial body weight. Muscle wasting with reduced subcutaneous fat were noticed. The skin was pale, and eyes displayed congested conjunctiva. No external traumatic lesions nor decubital ulcers were recorded.

INTERNAL EXAMINATION

The brain, lungs and liver were unremarkable except for severe congestion as a universal finding. Trivial amounts of serous effusion were found in the intrapericardial, intraperitoneal, and intrapleural cavities. The entire tongue was lined with yellowish white color extending downwards over the wall of the esophagus (Fig. 1). Subcutaneous and internal fat stores (e.g., omentum, mesentery, perirenal, and subepicardial area) were reduced and dark yellowish in color (Fig. 2). All layers of the gastro-intestinal tract were thin with translucent walls. Foci of mucosal haemorrhages were noticed at the stomach. The lumen of intestinal tract was empty except for a small amount of greenish yellow fluid approximately 20 ml. Hemorrhagic areas in the gastric lining were noticed. Foam secretions were found within the cavity of the trachea. The cutting surface of both lungs exudes bloody foam secretions upon finger-pressure. The organs size and weight of brain, right and left lungs, heart and liver in comparison to the published reference values **(Sheikhazadi *et al.*, 2010; Westaby *et al.*, 2023)** are displayed in (**Table 1**). The heart was reduced in size, the pericardium was normal, but a pale white superficial spot was observed over the left ventricle which did not extend to the myocardium, the myocardium was dark brown, coronaries (seen at the outer surface) were prominent and pericardial fat is replaced by oedematous tissue (signs of brown atrophy) (Fig.3). Dissection of the heart showed presence of mild to moderate stenosis at coronaries (Fig. 4). The liver showed dark reddish and granulated outer surface with solid consistency (Fig. 5) and the gall bladder was distended. Representative samples from heart, lung and liver were taken for histopathological examination.

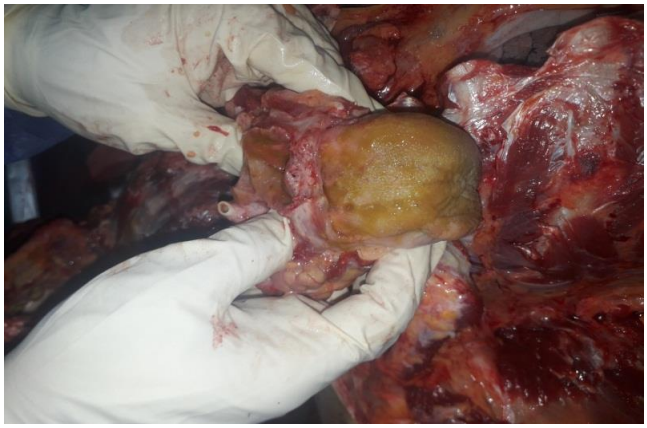

Figure 1: The tongue surface demonstrated a yellowish coating.

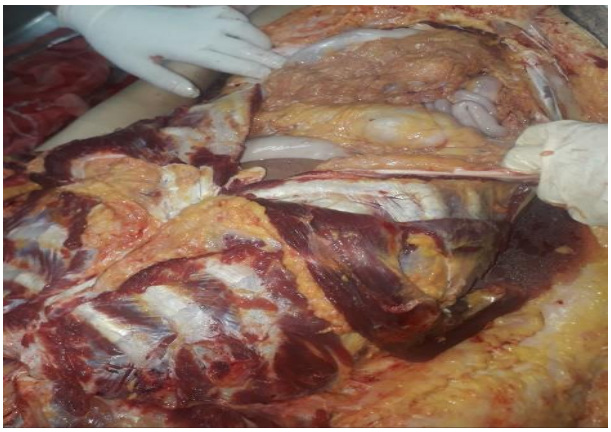

Figure 2: The body fat stores were present and dark yellowish in color.

Table 1: Comparison of Organ Weights (formalin fixed) with Reference Values.

Organ	Weight in grams	Mean organ weight [13] according to age*male sex	Organ weight [13] (in relation to male height)	Organ weight [13] (in relation to male BMI)
Brain	1430	1324.9 ± 108.4	1342.0 ± 111.1	1322.6 ± 115.8
Liver	2000	1545.0 ± 293.1	1594.0 ± 356.7	1457.0 ± 240.4
Right lung	790	582.3 ± 148.8	607.9 ± 175.2	551.5 ± 147.8
Left lung	670	545.3 ± 145.6	561.7 ± 154.2	528.1 ± 229.6
Heart	360	369.5 ± 74.2	365.1 ± 69.1	351.0 ± 74.1

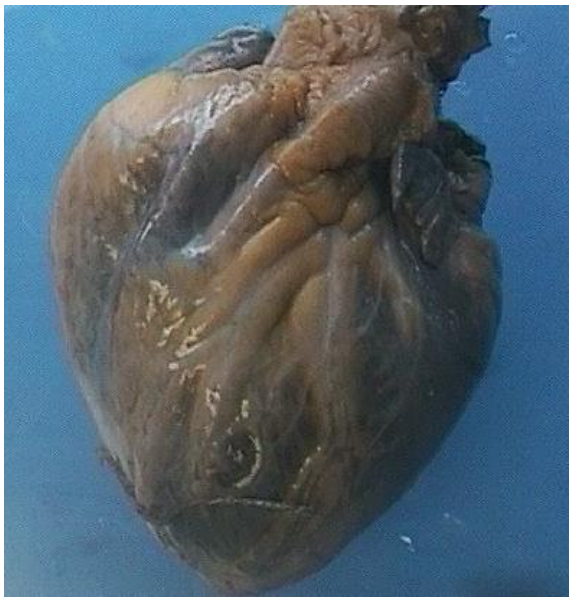

Figure 3: Gross Picture Of The Heart Showing Signs Of Brown Atrophy Of The Heart

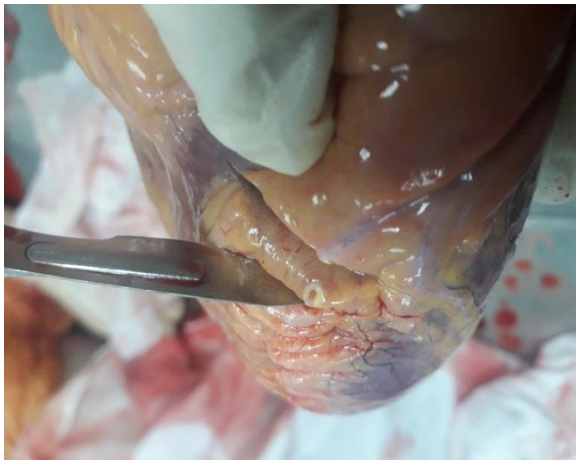

Figure 4: The Heart Was Grossly Unremarkable And The Coronary Arteries Arise From Their Normal Sites. The Cut Sections On The Coronary Arteries Showed Narrow Lumen With Yellow Colored Wall Due To Atheromatous Changes.

Figure 5: Gross Picture of The Liver Showing Pale Liver Sections and Congested Vessels.

HISTOPATHOLOGY

The brain, heart, pulmonary, and gastric tissue specimens showed marked dilation of the interstitial blood vessels and RBCs filling of superficial blood vessels in the sub-arachnoid area, pericardium, alveolar blood capillaries, and superficial mucosal layers, respectively (Fig. 6). The left anterior descending, left circumflex, and right coronary arteries showed moderate stenosis due to atheromatous changes with narrowness that were 70%, 50%, and 40%, respectively. Transverse cut section of the cardiac muscle has a thickness of 10 mm for each of the lateral left ventricular and septal walls whereas the thickness of the right ventricle wall was 3 mm. (Fig. 7). Sections from both lungs showed capillary congestion and atrophic emphysema; thick interstitial pulmonary blood vessels (diabetic vasculopathy) were also noticed (Fig. 8). The liver showed severe hepatic steatosis with hepatocyte degeneration and vacuolization. Severe congestion and dilation in the liver sinusoids and central veins in addition to interstitial blood vessels in the portal areas of the liver, severe

macrovascular steatosis, degenerative changes and intracellular deposits of pigment granules) (Fig. 9&10).

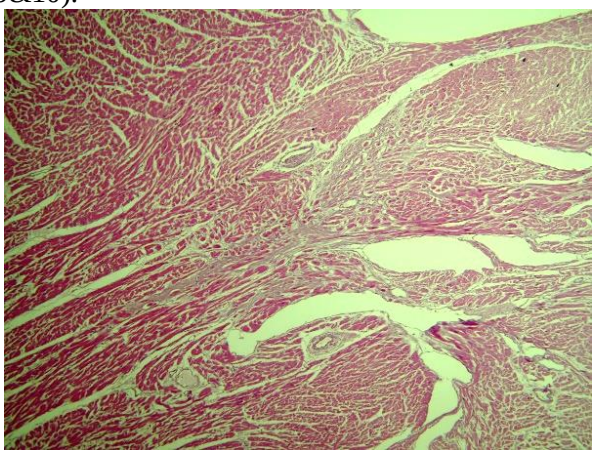

Figure 6: Microscopic Picture From Heart Section Showing Cellular Shrinkage And Focal Interstitial Myocardial Fibrosis In The Myocardium (H&E X10).

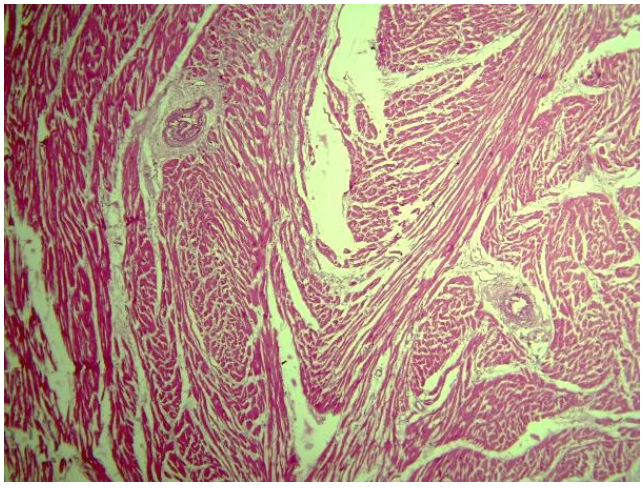

Figure 7: Microscopic Picture From Heart Section Showing Thick Interstitial Blood Vessels Of The Myocardium (Diabetic Vasculopathy) (H&E X10).

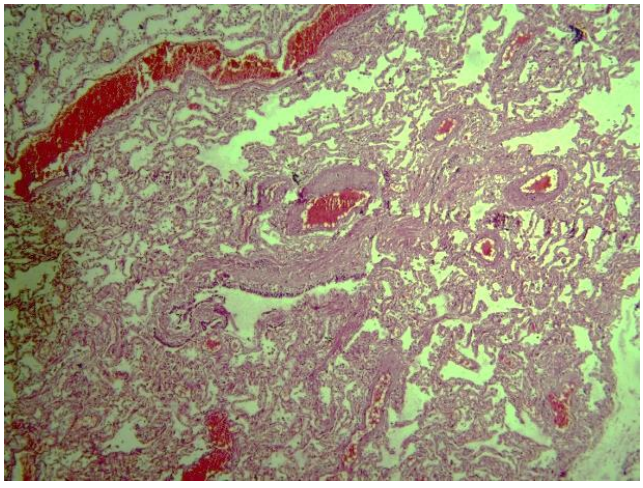

Figure 8: Microscopic Picture From Lung Section Showing Capillary Congestion And Thick Interstitial Pulmonary Blood Vessels (H&E X10).

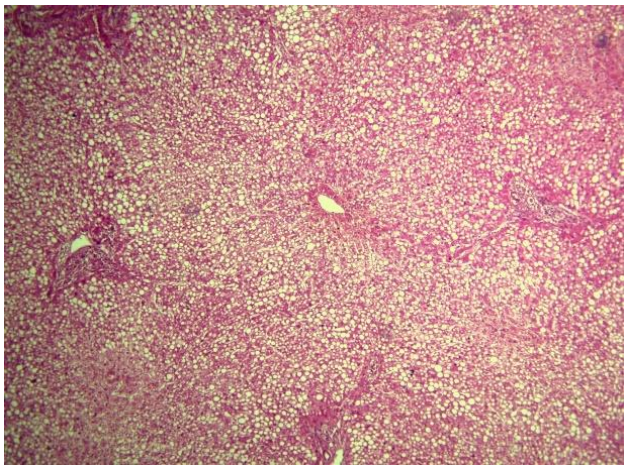

Figure 9: Microscopic Picture from Liver Section Showing Wide Areas Of Macrovascular Steatosis And Congestion (H&E X10).

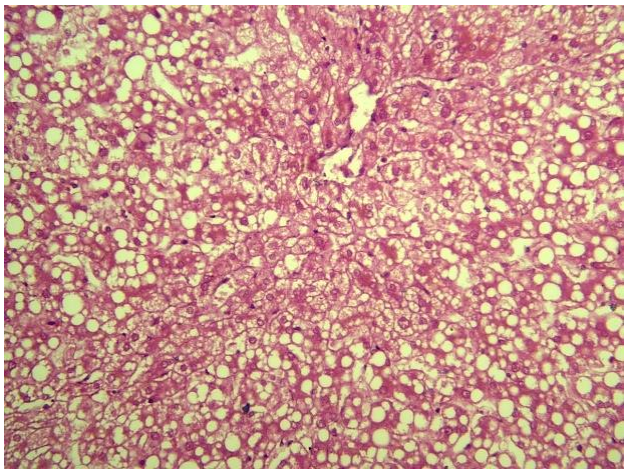

Figure 10: Microscopic Picture from Liver Section Showing Intracellular Large Vacuoles With Displaced Nuclei, Degenerative Changes In Some Cells And Intracellular Deposits Of Pigment Granules) (H&E X20).

TOXOCOLOGICAL AND BIOCHEMICAL ANALYSIS

Samples from blood, contents of stomach and stomach wall were sent to the chemical lab indicated negative results for narcotic and major and minor tranquilizers in addition to antidepressants, stimulants, cannabis, tramadol, and insecticides. Sample from the vitreous fluid of the eye indicated high glucose level of 325 mg/dl and positive detection of ketone bodies.

DISCUSSION

This is the foremost detailed case study of the longest documented period of voluntary starvation in a previously obese diabetic patient. Voluntary starvation deaths are uncommon, In Arab countries,

the prevalence remains low, primarily occurring in regions with political conflicts, as well as among homelessness and drug-addiction **(Abdellah, Ghandour and Ali, 2018; Graham, 2020).** In Egypt, a three-year study found only two cases (0.39%) with an average age of 35.5±14.8 years **(Abdellah, Ghandour and Ali, 2018).** Suzuki et al. (2013) reported that pure starvation deaths constituted only about 10% of all deaths **(Suzuki *et al.*, 2013)**. A complete lack of food and nutritional supplements typically leads to death within 45–73 days, with an average of 61.6±2.5 days in non-obese young individuals **(Júnior, 2018)**. Vitamin supplements can extend survival up to 115 days (**Kirbas *et al.*, 2008)**. In our case we reported the survival of the deceased on fluid-only diet for 2 years. In obese individuals, starvation dieting, particularly among diabetics, is documented to extend survival beyond one year **(Mazur, 2011)**. Additionally, Stewart et al. (1973) reported successful therapeutic starvation for 382 days in a morbidly obese person supported by multivitamin supplements and non-caloric fluids **(Stewart and Fleming, 1973)**. This could explain the extended survival period in our case, influenced by obesity and juice-only diet.

Cases of starvation due to suicide and political hunger strikes differ significantly in terms of motivation, context, and societal impact **(Miller, 2016, 2017)**. Those who choose starvation as a method of suicide often do so out of profound personal despair or psychological distress, seeing it as a means to escape their suffering. This act is usually solitary and not intended to elicit a broader societal response **(Miller, 2017)**. On the other hand, political hunger strikes are deliberate acts of protest meant to highlight social injustices or oppressive conditions. Participants use their own bodies as tools of resistance, aiming to pressure authorities into addressing their demands, such as better prison conditions or political recognition **(Miller, 2016)**. While both forms of starvation can lead to death, political hunger strikes are part of a larger narrative of activism and collective struggle, often attracting public support and international attention, as seen in the cases of Bobby Sands and Orlando Zapata Tamayo **(Miller, 2016).** The key difference lies in the motivation behind the act—individual despair versus collective resistance—and the level of societal engagement that political hunger strikes typically provoke.

The typical signs of dehydration in starvation, such as sunken eyes, scaphoid abdomen, and prominent bones, might be absent due to high water consumption, given water calorie-free nature. However, significant gastrointestinal changes, like hemorrhagic gastroenteropathy, occur due to glutamine deficiency from the small intestinal lumen **(Altun *et al.*, 2004; Garland and Irvine, 2022).** A yellow tongue and esophageal coating are often seen in oral candidiasis cases, which are associated with Type II diabetes as an inflammatory response to hyperglycemia **(Hammad, Darwazeh and Idrees, 2013)**. Internally, the liver showed hepatic steatosis due to prolonged protein deficiency **(Garland and Irvine, 2022)**. The intestines were empty, and the gallbladder was distended due to the lack of food to stimulate bile secretion **(Madea, Ortmann and Doberentz, 2016).**

Previous studies have shown a strong positive correlation between the weights of the heart and liver with body height and BMI, while the correlation for the lungs and other organs is weak or non-significant **(Sheikhazadi *et al.*, 2010; Westaby *et al.*, 2023)**. Lung weights vary in relation to starvation due to biological sex and the terminal event before death, such as congestive heart failure, pulmonary edema/congestion, and malnutrition-related infection. In our case, the liver weight and other internal organs, excluding the heart, were increased compared to the reference data for sex, age, and height **(Sheikhazadi *et al.*, 2010; Westaby *et al.*, 2023**). This is consistent with generalized severe congestion in the brain, liver, and both lungs. The heart weight and thickness of the left ventricular and septal walls were slightly below normal reference data, this cardiac muscle wasting is possibly due to prolonged fasting (Sheikhazadi *et al.*, 2010). The combination of long-term starvation and diabetes mellitus presents a challenge for clinicians and forensic pathologists. In this case, two mechanisms of metabolic acidosis were involved. A decrease in the insulin-glucagon ratio in a glycogen-depleted environment can worsen or cause hyperglycemia due to starvation-induced insulin resistance associated with hepatic steatosis, increased ketone body formation, and severe metabolic acidosis **(Espes *et al.*, 2013; Boutin and Laskine, 2016)**. The significant reduction in blood albumin, combined with prolonged hepatic metabolism of FFAs to KBs, leads to structural abnormalities in extrahepatic insulin receptors and severe hepatic dysfunction in the mitochondria, peroxisome, and fat aggregation inside liver cells, resulting in hepatic steatosis and liver cell degeneration **(Sahani, Itakura and Mizushima, 2014; van Zutphen *et al.*, 2016; Yeow *et al.*, 2016; Iwata *et al.*, 2017).**

In pure starvation, vitreous humor biochemical analysis typically shows hypo- or euglycemia depending on the BMI, whereas DKA causes hyperglycemia **(Chen *et al.*, 2015; Palmiere *et al.*,**

2016). Hyperglycemic DKA with a fatal outcome is diagnosed by detecting elevated vitreous glucose >13 mmol/L (234 mg/dL) and positive ketone bodies **(Karlovsek, 2004)**. According to Zilg et al., a vitreous glucose concentration >10 mmol/L (180 mg/dL) corresponds to antemortem blood glucose concentrations of approximately 26 mmol/L (468 mg/dL)(**Zilg *et al.*, 2009)**. In this study, the vitreous glucose concentration was 18 mmol/L (325 mg/dL), exceeding the fatal level.

Ultimately, the deceased developed starvation-related insulin resistance alongside the known insulin-resistant state of Type II diabetes **(Koffler and Kisch, 1996; Duška *et al.*, 2005). He co**ntinued to develop ketosis despite exogenous insulin administration, leading to significant metabolic decompensation due to prolonged starvation **(Wang *et al.*, 2015**). Cardiac arrest likely resulted from sudden arrhythmia secondary to electrolyte disturbances associated with DKA.

The hallmark of starvation and DKA management involves the abrupt shift from a low insulin, fat-burning metabolism to a high insulin, glucose-based state. Refeeding syndrome is a well-recognized, potentially fatal complication of high-caloric nutrition in severely malnourished individuals, resulting in metabolic and biochemical changes due to rapid intracellular electrolyte shifts of phosphorus, potassium, and magnesium with increased insulin and blood glucose levels **(Crook, 2014; Kitajima *et al.*, 2022)**. In refeeding syndrome, these complications typically occur within the first few days to the first week after refeeding, whereas DKA is usually fatal within 1 to 2 days of symptom onset **(Smith and Elia, 2006; Crook, 2014; Siregar *et al.*, 2018; Kjærulff and Astrup, 2019; Kitajima *et al.*, 2022).** DKA Management is similar to refeeding syndrome. When exogenous insulin therapy is used to manage DKA, it introduces glucose and electrolytes into the cells, causing blood electrolyte levels to drop, necessitating supplementation due to the accelerated refeeding response once glycemic control is achieved **(Matz, 1994; Mehanna *et al.*, 2009).** This study possesses several strengths. It provides a comprehensive and detailed case study of the longest documented period of voluntary starvation in a previously obese diabetic patient, The interdisciplinary analysis combines forensic pathology, endocrinology, and nutrition, illustrating the complex interplay between prolonged starvation and diabetes mellitus. However, it is limited by the fact that postmortem biochemical analyses may not fully capture the dynamic physiological changes that occurred during the starvation period. Future research should focus on investigating the role of nutritional supplements and interventions during prolonged starvation which could offer valuable insights into potential therapeutic strategies for managing similar cases.

CONCLUSION

This is the foremost detailed case study of the longest documented period of voluntary starvation in a previously obese diabetic patient. The cause of death is ketoacidosis secondary to the combined effects of diabetes mellitus and starvation.

RECOMMENDATION

Future research should focus on potential therapeutic strategies for managing similar cases. Also, Much research to be emphasized on contribution of such medical conditions on the actual cause of death.

CONFLICT OF INTEREST

The authors declare that they have no competing interests

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الملخص العربي

"كيف يؤثر الجوع لفترات طويلة على الحماض الكيتوني المميت لدى مرضى السكري؟ رؤى من دراسة حالة تشريحية"

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الخلفية: المجاعة الطوعية هي سبب نادر للوفاة، إن الفهم الكامل لكيفية تفاعل الأمراض المصاحبة للوفاة أمر بالغ الأهمية لتوصيف الاسباب المرضية الحقيقية للوفاة. **الهدف**: في تقرير هذه الحالة، نناقش ونوضح العلاقة المتشابكة بين الجوع لفترات طويلة ومرض السكري، حيث يوضح تقرير الوفاة قدوم رجل يبلغ من العمر ٤٩ عامًا قام بحجب الطعام طواعية، ولكنه استهلك السوائل لمدة عامين تقريبًا. تم إدخاله إلى المستشفى بسبب تغيب عن الوعي وتوفي بعد حوالي ٤٨ ساعة. النتائج: كشف تحليل الجسم الزجاجي للعين بعد الوفاة عن وجود الاحماض الكيتونية وارتفاع بمستوى الجلوكوز ٣٢٥ ملغم / ديسيلتر والذي تجاوز المستوى المميت الذي يبلغ > ٢٣٤ ملغم / ديسيلتر. كشفت التشريح المرضي عن تغيرات في الشرايين التاجية مع تضييق معتدل مع اعتلال الأوعية الدموية الموصوف في الداء السكري، كما أظهر الكبد مناطق واسعة من تنكس دهني بالأوعية الدموية الكبيرة، وبعض التغيرات الخلوية. وكان الصيام المطول مصحوبًا بنقص الأنسولين وزيادة مقاومة الأنسولين، وهو ما لم يتم عكسه عن طريق العلاج في المستشفى. **الاستنتاج**: عدم وجود نتائج مرضية أو سمية مميتة أخرى يشير إلى أن حالة الجوع المتعمد أدت إلى تفاقم حالة مرض السكري ومقاومة الأنسولين، وأن تصلب الشرايين التاجية المعتدل ليس السبب المباشر للوفاة، ولكنه يعزز الحالة النهائية. فكان ارتفاع الاحماض الكيتونية الشديد غير المستجيب للعلاج بالأنسولين مع مدة قصيرة من العرض السبب المؤدي للوفاة.