# A Novel Unusual Manifestation of CH-Alpha as Acute Metabolic Disturbances: Case Report and Big Data Analytics

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## Introduction:

There are myriads of dietary and nutritional supplements available in the factual and virtual markets of the pharmaceutical industry [1, 2]. Consumers are avid to take those chemicals as complements to their regular diet to boost their health status, sexual endurance, physical performance, or even their cognitive abilities [3, 4]. Health authorities such as the World Health Organization, Food and Drug Administration in the United States, United Nations Office on Drugs and Crime, European Monitoring Centre for Drugs and Drug Addiction, and the Global Public Health Intelligence Network should regulate all chemicals [5]. Although there is an abundance of regulating and controlling agencies, an immense amount of unregulated or illegal chemicals, including supplements, exist either in the black market or virtually across the web [1, 3, 6-8]. Illegal trading activities require anonymity that flourishes in the developing nations and electronically, via electronic commerce, over the darknet marketplace [6-8]. In 2008, "Satoshi Nakamoto" created the first decentralized digital currency system in the world, known as bitcoin [9]. The advent of cryptocurrencies was essential for untraceable illegal trade activities over the internet [10].

Some studies and clinical trials also claim evidence on the beneficial effect of supplements for systemic abnormalities including musculoskeletal conditions, joint pathologies, and degenerative joint diseases [11, 12]. Chondroitin sulfate, hyaluronic acid, and collagen hydrolysate can maintain and rejuvenate the articular cartilages in patients with degenerative joints disease, for instance, in osteoarthritis and rheumatoid arthritis [13, 14]. GELITA, a pharmaceutical company founded in 1875 in Germany, is well-known for manufacturing supplements of regenerative potentials for patients with articular and joint pathologies [15]. GELITA has over 696 million euros in revenue, more than twenty-one plant products, sales offices worldwide, and about 2,500 employees worldwide [15]. The enterprise promoted several products worldwide including FORTIGEL, CH-Alpha, and CH-Alpha Plus [15]. In Iraq, pharmacies are selling CH-Alpha and CH-Alpha Plus in the range of 55-65 United States Dollars (Figure 1). Legend Drug Store in Amman [Jordan] is the exclusive supplier of these products to Iraq [16]. The main difference between the Plus version and regular CH-Alpha is that the former contains additional ingredients such as the rosehip extract, selenium, and vitamin D [15, 16].

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**CH-Alpha**

| Ingredient per 25ml | Amount per serving | المكونات لكل ٢٥ مل |
|---|---|---|
| **Active ingredients:**<br>Collagen Hydrolysate( Fortigel®)<br>Vitamin C | <br>10000 mg<br>90 mg | **المواد الفعالة :**<br>كولاجين هيدرولايزيت (فورتيجل)<br>فيتامين ج |
| **Other ingredients:**<br>Water, Fructose, Citric Acid, Color (malt extract), Preservatives (Potassium Sorbate), Flavor Sweeteners (Acesulfame and sucralose | | مكونات أخرى:<br>ماء، مادةفركتوز (سكرالفواكه) ،لون مفتطف الشعير، حمض الليمون، مواد حافظة<br>(بوتاسيوم سوربات)، نكهة، محلي (سكر اللوز + اسيسولفام).- الكمية المسموح تناولها<br>يوميأ من الحلي ١٥ ملجم/كغم من وزن الجسم |

**Recommended dose:** Shake well before opening and Drink one vial daily at night or as directed by your physician.

**Warnings:** Keep out of reach of children. Do not exceed the recommended daily dose. Store in cool dry place away from direct sun exposure and avoid excessive heat (below 30 °C).

**Indication:** Promotes Joints and Cartilage Health.

**CH-Alpha PLUS**

| Ingredient per 25ml | Amount per serving | المكونات لكل ٢٥ مل |
|---|---|---|
| **Active ingredients:**<br>Collagen Hydrolysate( Fortigel®)<br>Vitamin C<br>Rose hip extract<br>Vitamin D<br>Selenium | <br>5000 mg<br>90 mg<br>500 mg<br>200 IU<br>55µg | **المواد الفعالة :**<br>كولاجين هيدرولايزيت (فورتيجل)<br>فيتامين ج<br>مستخلص ثمرة الورد<br>فيتامين د<br>سيلينيم |
| **Other ingredients:**<br>Water, Fructose, Citric Acid, Color (malt extract), Preservatives (Potassium Sorbate), Flavor Sweeteners (Acesulfame and sucralose | | مكونات أخرى:<br>ماء، مادةفركتوز (سكرالفواكه) ،لون مفتطف الشعير، حمض الليمون، مواد حافظة<br>(بوتاسيوم سوربات)، نكهة، محلي (سكر اللوز + اسيسولفام).- الكمية المسموح تناولها<br>يوميأ من الحلي ١٥ ملجم/كغم من وزن الجسم |

**Recommended dose:** Shake well before opening and Drink one vial daily at night or as directed by your physician.

**Warnings:** Keep out of reach of children. Do not exceed the recommended daily dose. Store in cool dry place away from direct sun exposure and avoid excessive heat (below 30 °C).

**Indication:** Promotes Joints and Cartilage Health.

**Figure (1) CH-Alpha in Iraqi Pharmacies: CH-Alpha and CH-Alpha Plus.**
† Manufacturer: GELITA Health GmbH [Eberbach, Germany].
†† Supplier: Legend Drug Store [Amman, Jordan].

We are reporting a case of acute metabolic disturbances in association with the ingestion of CH-Alpha. We shall also implement statistical inference in combination with prediction, via substantiative data from the Google search engine, to augment the validity of our study. Prediction, via regression analytics as a modality of machine learning, can provide reliable data on future trends for time-series analysis in connection with the interest of web users in these products [17-22]. There have previous attempts to conduct real-time investigations based on Google-derived data to map the spatial and temporal variations within big data of interest [23, 24]. We shall also interpret our case, for assessing the presumed causality, using the renowned Bradford Hill's criteria [25].

**Case Report**
A thirty-five years old male, by the pseudonym "Ronald Fisher", who was healthy and physically fit apart from facet joints degeneration of the lumbar spine, took an over-the-counter supplement known as CH-Alpha. He presented to a private internal medicine specialty clinic in Baghdad during November 2019. The patient ingested three vials of the medication, at the rate of one vial each day, after which he developed some alarming clinical manifestations. Precisely, two days following the ingestion of the first vial of CH-Alpha, the patient presented with early-morning bilateral peri-orbital edema and late-day dependent bilateral leg edema limited mainly to the region of the foot and the ankle. Those presentations increased in severity during the following days. The patient also noticed a gradual gain in body weight from 70 to 75Kg over a few days during which he became symptomatic. The patient principally complained from an occipital headache that could persist for hours, which he described to be throbbing in nature. Within a few days, the headache became more generalized over the head and resistant to all sorts of painkillers and prevented the patient from sleeping. Within one week from the appearance

of those symptoms, the patient decided to visit a physician. The physician conducted a comprehensive examination, biochemical profiling, and radiologic investigations, including echocardiography and abdominal ultrasonography. Clinical examination, including neurological assessment, was normal apart from the oedematous manifestations that persisted for three weeks and made the patient very anxious. Biochemical profiling revealed hypoproteinemia (6.5 g/dl), hypogammaglobulinemia (1.58 g/dl) while serum albumin levels were normal (4.92 g/dl). "Ronald Fisher" had normal levels of C-reactive protein (i.e., negative), ESR (10 mm/hr), and serum Uric acid (4.5 mg/dl). His lipid profile was unexpectedly abnormal, albeit being physically fit and a former athlete with an average body-mass index (BMI=20.2). He had a borderline high level of serum cholesterol and LDL (218 mg/dl and 159.3 mg/dl, respectively), a marginal risk level for HDL (36.3 mg/dl) while serum triglycerides and VLDL were within the acceptable range (112 mg/dl and 22.4 mg/dl, respectively). There were no aberrations of the liver and renal function tests, except for borderline serum creatinine level (1.2 mg/dl). The complete blood picture, differential white blood cells, acute phase reactants, complement profile, and general urine examination (GUE) were typical of a healthy person. The patient also had a standard 24-hour urine collection (volume=1380 milliliters) with no microalbuminuria (10 mg/24 hours). There were no abnormalities in the chest X-ray, echocardiography, and abdominal ultrasonography. The clinical and biochemical pictures were suggestive of acute hepatic impairment, involving the protein metabolism as well as lipid-apoproteins biosynthesis pathway, culminating in an overloading renal apparatus. Fortunately, Mr. "Fisher" recovered spontaneously and gradually over three weeks following the ingestion of the last (third) vial of CH-Alpha.

**Discussion:**

**The Literature:** During December 2019, we conducted a systematic review of the medical and paramedical databases of the peer-reviewed literature in an attempt to detect publications concerning our presented case (Figure 2). We searched the Cochrane Library [the Cochrane Database of Systematic Reviews/the Cochrane Collaboration], PubMed [the United States National Library of Medicine], and Embase [Elsevier Database/Scopus]. We deployed an exhaustive composite of MeSH-based keywords and generic terms, as well as truncations, and shuffling those using Boolean operators. We included keywords related to four main themes including dietary supplements for joints pathologies, metabolic disturbances, clinical features, and epidemiology. The review strategy generated a total count of 565,641 papers distributed as follows: the Cochrane Library of Systematic Reviews [7,173; 1.27%], the United States National Library of Medicine [440,154; 77.82%] and Embase [118,314; 20.92%]. Based on the combination of all themes of keywords, the total number of publications was 55,482, allocated as follows: the Cochrane Library [0.0], United States NLM [0.0], and Embase [55,482; 100.00%] (Figure 2). Most of the publications were indexed in PubMed databases. Embase represented noisy false-positive data signals, i.e., publications that were not relevant to our keywords-based search strategy. Accordingly, we concluded that there are no relevant publications in connection with acute metabolic disturbances in association with the ingestion of CH-Alpha, CH-Alpha Plus, or related products such as FORTIGEL.
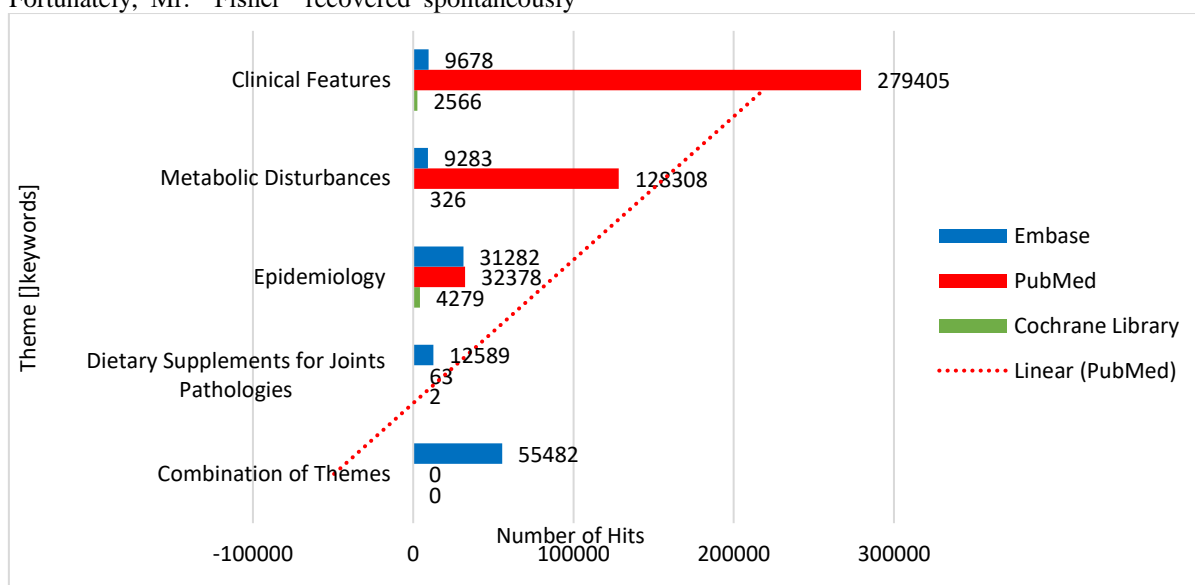


**Figure (2) Review of the Literature.**
† Timestamp: 9th, December 2019.

**Google-Based Analytics:** Using big data from Google search engine, specifically Google Trends, we mapped the interest of users of the surface web in CH-Alpha, FORTIGEL ingredients of CH-Alpha and the manufacturing company, GELITA. We retrieved longitudinal data (2004-2019) concerning the

temporal and geographic variations using three keywords CH-Alpha, FORTIGEL, and GELITA (Figures 3 and 4). Twenty three nations contributed to the holistic geographic map, most of them were from the developed world, Latin countries, and Far East Asia. Data signals were absent from the north of Africa and the Middle East, except for Turkey. Those countries included New Zealand, Sweden, South Africa, Australia, the Netherlands, Malaysia, Taiwan, Colombia, Thailand, Indonesia, the United Kingdom, Canada, Vietnam, India, Brazil, Mexico, Chile, the United States, Germany, France, Italy, Spain, and Turkey (Figure 3). On a percentile scale, the interest of surface web users revealed high variability with time concerning CH-Alpha 5.07 (+/- 0.37), FORTIGEL 3.55 (+/- 0.26), and GELITA 33.07 (+/- 2.39) (Table 1 and Figure 4). Surface web users were most interested in GELITA patented products, which peaked in May 2004. Statistical outliers existed in three consecutive years: 2004 (April-October), 2005 (February and September), and 2006 (January,

February, May, and December). Interest in GELITA products followed a polynomial equation ($R^2$ score= 0.556; Coefficient of Correlation= 0.746) (Figure 4). The polynomial curve estimation is useful for predictive analytics with some margin of error. Statistical inference, implementing the Univariate Analysis of Variance, confirmed a statistically significant difference in favor of GELITA (df= 2; F= 775.405; *P*-value<0.001; Partial Eta Squared=730; Adjusted R Squared= 0.729) (Table 1). Post-Hoc testing, relying on Bonferroni's correction, indicated a statistically significant difference between GELITA versus CH-Alpha (mean difference= 28.00; Cohen's d= 2.82; *P*-value<0.001; 95% Confidence Interval= 25.97-30.03), and GELITA versus FORTIGEL (mean difference= 29.52; Cohen's d= 3.14; *P*-value<0.001; 95% Confidence Interval= 27.49-31.55), whereas there was no significant difference between CH-Alpha versus FORTIGEL (mean difference= 1.52; Cohen's d= 0.36; *P*-value=0.216; 95% Confidence Interval= -0.51-3.55) (Table 1).

**Table (1) Univariate Analysis of Variance and Post-Hoc Testing**

**Univariate Analysis of Variance**

**Descriptive Statistics**

Dependent Variable:  Interest [surface web]

| Keyword | Mean | Std. Deviation | No. |
|---|---|---|---|
| CH-Alpha | 5.07 | 5.291 | 192 |
| FORTIGEL | 3.55 | 2.898 | 192 |
| GELITA | 33.07 | 12.995 | 192 |
| Total | 13.89 | 15.896 | 576 |

**Tests of Between-Subjects Effects**

Dependent Variable: Interest [surface web]

| Source | Type III Sum of Squares | Df | Mean Square | F | Sig. | Partial Eta Squared |
|---|---|---|---|---|---|---|
| Corrected Model | 106098.722ᵃ | 2 | 53049.361 | 775.405 | .000 | .730 |
| Intercept | 111194.460 | 1 | 111194.460 | 1625.293 | .000 | .739 |
| Keyword | 106098.722 | 2 | 53049.361 | 775.405 | .000 | .730 |
| Error | 39201.818 | 573 | 68.415 | | | |
| Total | 256495.000 | 576 | | | | |
| Corrected Total | 145300.540 | 575 | | | | |

a. R Squared = .730 (Adjusted R Squared = .729)

**Post Hoc Tests**

**Multiple Comparisons**

Dependent Variable:   Interest [surface web]

Bonferroni

| (I) Keyword | (J) Keyword | Mean Difference (I-J) | Std. Error | Sig. | 95% Confidence Interval Lower Bound | Upper Bound |
|---|---|---|---|---|---|---|
| CH-Alpha | FORTIGEL | 1.52 | .844 | .216 | -.51 | 3.55 |
| | GELITA | -28.00* | .844 | .000 | -30.03 | -25.97 |
| FORTIGEL | CH-Alpha | -1.52 | .844 | .216 | -3.55 | .51 |
| | GELITA | -29.52* | .844 | .000 | -31.55 | -27.49 |
| GELITA | CH-Alpha | 28.00* | .844 | .000 | 25.97 | 30.03 |
| | FORTIGEL | 29.52* | .844 | .000 | 27.49 | 31.55 |

Based on observed means.
 The error term is Mean Square(Error) = 68.415.

*. The mean difference is significant at the .05 level.

† Interest of Surface Web Users [Google Trends: 01.01.2004 — 01.01.2020].

†† Statistical Analysis via the Statistical Package for Social Sciences [SPSS v.24]



**Figure (3) Geographic Mapping of Interest in CH-Alpha.**
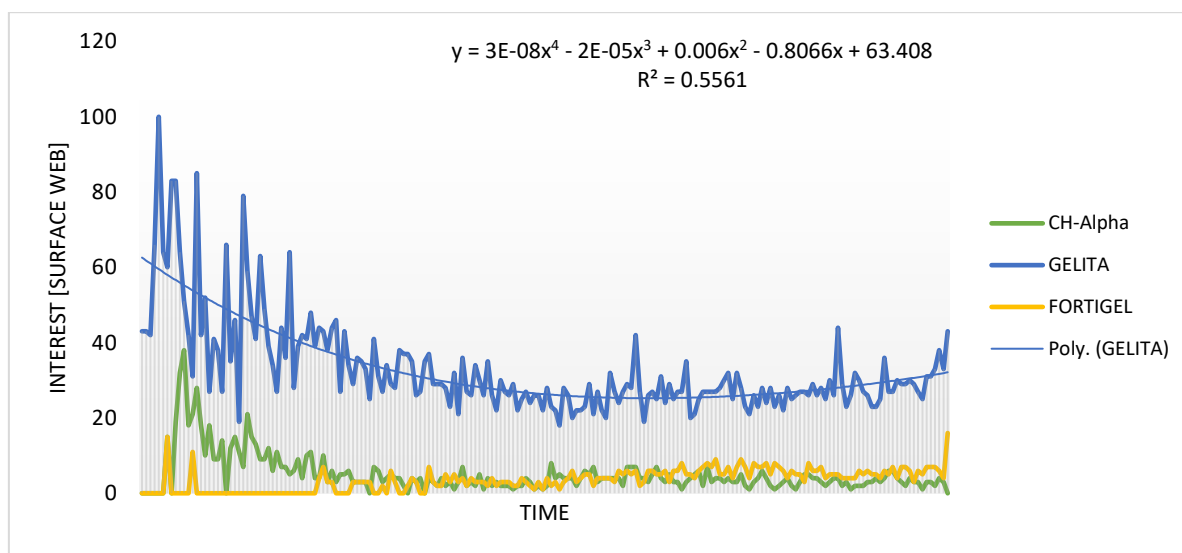† Interest of Surface Web Users [Google Trends: 01.01.2004 — 01.01.2020].

$$y = 3E\text{-}08x^4 - 2E\text{-}05x^3 + 0.006x^2 - 0.8066x + 63.408$$
$$R^2 = 0.5561$$

**Figure (4): Temporal Variation of Interest in CH-Alpha.**

**Interpretation: Bradford Hill's Criteria**: In 1965, British statistician Austin Bradford Hill proposed nine elements-based criteria to provide evidence for the understanding of causality between a potential effect and an observed outcome [25]. Hill demands analysis of the strength of association and effect size, the reproducibility of results, the specificity of association, the temporality of causation, the gradient effect, i.e., a dose-response relationship, plausibility, coherence, experimental validation, and analogy [25]. Some authors also added reversibility to Hill's criteria as the tenth element [26]. Our case can satisfy five items out of ten of Hill's criteria. including temporality, gradient effect, plausibility, analogy, and reversibility, i.e., half of the full spectrum of Bradford Hill's criteria. Nonetheless, our case represents an anecdotal report in which ambiguous co-variables could have interfered. Future studies should deploy higher-hierarchial level-of-evidence experiments, including prospective and randomized controlled trials, to prove our assumption on the causality of CH-Alpha and acute protein-lipid dysmetabolism. Again, by referring to the Bradford Hill's criteria, it is plausible to incriminate this dietary supplement given its high-protein content in the form of collagen hydrolysate [10000 mg in CH-Alpha and 5000 mg in CH-Alpha Plus] (Figure 1). Other ingredients, including the rosehip extract and selenium, might also play a role as cofactors in combination with collagen, to induce metabolic or immune-mediated metabolic disturbances in humans.

**The Level of Evidence:** According to the Oxford Centre for Evidence-based Medicine (OCEBM), our study represented an observational data analytic [27, 28]. However, it represented an amalgam of a case report and internet snapshots (Grade C), and longitudinal analyses of big data via the database of literature and trends (Grade D) [28]. Accordingly, we cannot categorize the level-of-evidence for this study in correspondence with the existing categorization scheme imposed by the OCEBM in 2016 [27].

**Conflict of interest:** The authors declare that there are no conflicts of interest. The patient, to whom the case report belongs, consented this publication.

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أثار جانبية غير مسبوقه مترافقة مع دواء **CH-Alpha** كاضطرابات أيضية حادة
تقرير حالة وتحليل للبيانات الضخمة

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**الكلمات المفتاحية:** معايير برادفورد هيل؛ CH-ألفا؛ الوذمة؛ جيليتا؛ فورتيجيل؛ نقص غاماغلوبولين الدم؛ نقص بروتينات الدم.