INVITA IV DRIPS

BY LIQUIVIDA

IV Therapy
Science and
Articles Magazine

INVITA
IV VITAMINS THERAPY

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Why IV Drip Therapy

Numerous studies conducted over the decades have consistently demonstrated that enhanced nutrition can...

Nutrition plays a crucial role in promoting positive health outcomes for a wide range of symptoms, illnesses, and diseases. Research indicates that a deficiency in various nutrients can result in negative or severe health consequences. However, nutrition often remains underemphasized in the training of healthcare providers.

Interventional nutrition—where healthcare professionals use specific nutrients to enhance health or prevent disease—can now be administered safely through innovative methods such as intravenous therapy. I have personally administered this approach to many patients, achieving remarkable results due to the enhanced absorption of the formulated nutrients.

" We are at a time of great change when it comes to human health. We are beginning to see the foundations of a movement that transforms the way we approach and engage with our health services. IV drip therapy is part of this movement, aimed at improving wellness and satisfying health goals. It describes the administration of fluids and nutrients directly into the bloodstream, offering a faster way of delivery into the body."

Dr Michael Barnish

"As a doctor I'm truly humbled to have contributed to the development and growth of this industry in IV drip therapy. Over the past decade we've demonstrated that elective IV therapy can be delivered in a safe and effective manner to customers across the world, helping them achieve their health and wellness goals. Elective hydration and injectable supplementation, within a non-hospital setting are becoming more acceptable and IV therapy is now seen as an emerging industry by the world."

Dr Johnny Parvani MD

INVITA, Committed to Science

Life Science Division emerged from a strong desire.

 # Advancing the IV Therapy Industry

The goal is to enhance the IV therapy sector by investigating its effectiveness in improving health outcomes for individuals.

To illustrate this, REVIV conducted a comprehensive literature review and published a peer-reviewed scientific paper in the journal *Nutrients*. This paper delves into the significance of nutrient therapy in alleviating fatigue, particularly as a symptom associated with various diseases or illnesses. It systematically examines the scientific literature on different nutrients and their roles in addressing this symptom.

nutrients

an Open Access Journal by MDPI

Nutrient Therapy for the Improvement of Fatigue Symptoms

MichaelBarnish; Mahsa Sheikh; AndrewScholey

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Abstract: Fatigue, characterised by lack of energy, mental exhaustion and poor muscle endurance which do not recover following a period of rest, is a common characteristic symptom of several conditions and negatively impacts the quality of life of those affected. Fatigue is often a symptom of concern for people suffering from conditions such as fibromyalgia, chronic fatigue syndrome, cancer, and multiple sclerosis. Vitamins and minerals, playing essential roles in a variety of basic metabolic pathways that support fundamental cellular functions, may be important in mitigating physical and mental fatigue. Several studies have examined the potential benefits of nutrients on fatigue in various populations. The current review aimed to gather the existing literature exploring different nutrients' effects on fatigue. From the searches of the literature conducted in PubMed, Ovid, Web of Science, and Google scholar, 60 articles met the inclusion criteria and were included in the review. Among the included studies, 50 showed significant beneficial effects ($p < 0.05$) of vitamin and mineral supplementation on fatigue. Altogether, the included studies investigated oral or parenteral administration of nutrients including Coenzyme Q10, L-carnitine, zinc, methionine, nicotinamide adenine dinucleotide (NAD), and vitamins C, D and B. In conclusion, the results of the literature review suggest that these nutrients have potentially significant benefits in reducing fatigue in healthy individuals as well as those with chronic illness, both when taken orally and parenterally. Further studies should explore these novel therapies, both as adjunctive treatments and as sole interventions.

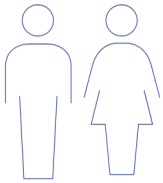
Scientific Work on Fatigue

One ofthe waysscientistsand doctors measure fatigueseverityis using the fatigue assessment scale, a scoring system that grades people and can help identify improvements after different interventions. we have been using this method to monitor our customer's energy levels with IV drip therapy. This compliments our published scientific paper, that explores nutritional therapies for the symptom of fatigue. Reviewing case studies with fatigue, we found that after just one treatment, many of our customers have improved fatigue assessment scale scores and many of them even have completely normal energy levels after. "Case studies are a vital part of science, often helping scientists and healthcare providers ask the right questions, helping to advance the process of science further."

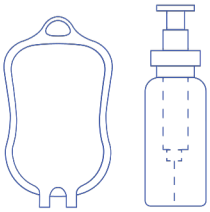
Dr Michael Barnish

Personalized Nutrition in Action

Monitoring the Effectiveness of Personalized IV Therapy for Customers Experiencing Fatigue and low energy symptoms. IVs personalized based on Liquivida's first published literature review in the journal Nutrients. Fatigue assessment scale score is an approved measure of fatigue symptom.



customers, aged 25-65 Male & Female Mixed ethnicities



Intervention: IV or IM therapy, personalized to their symptoms

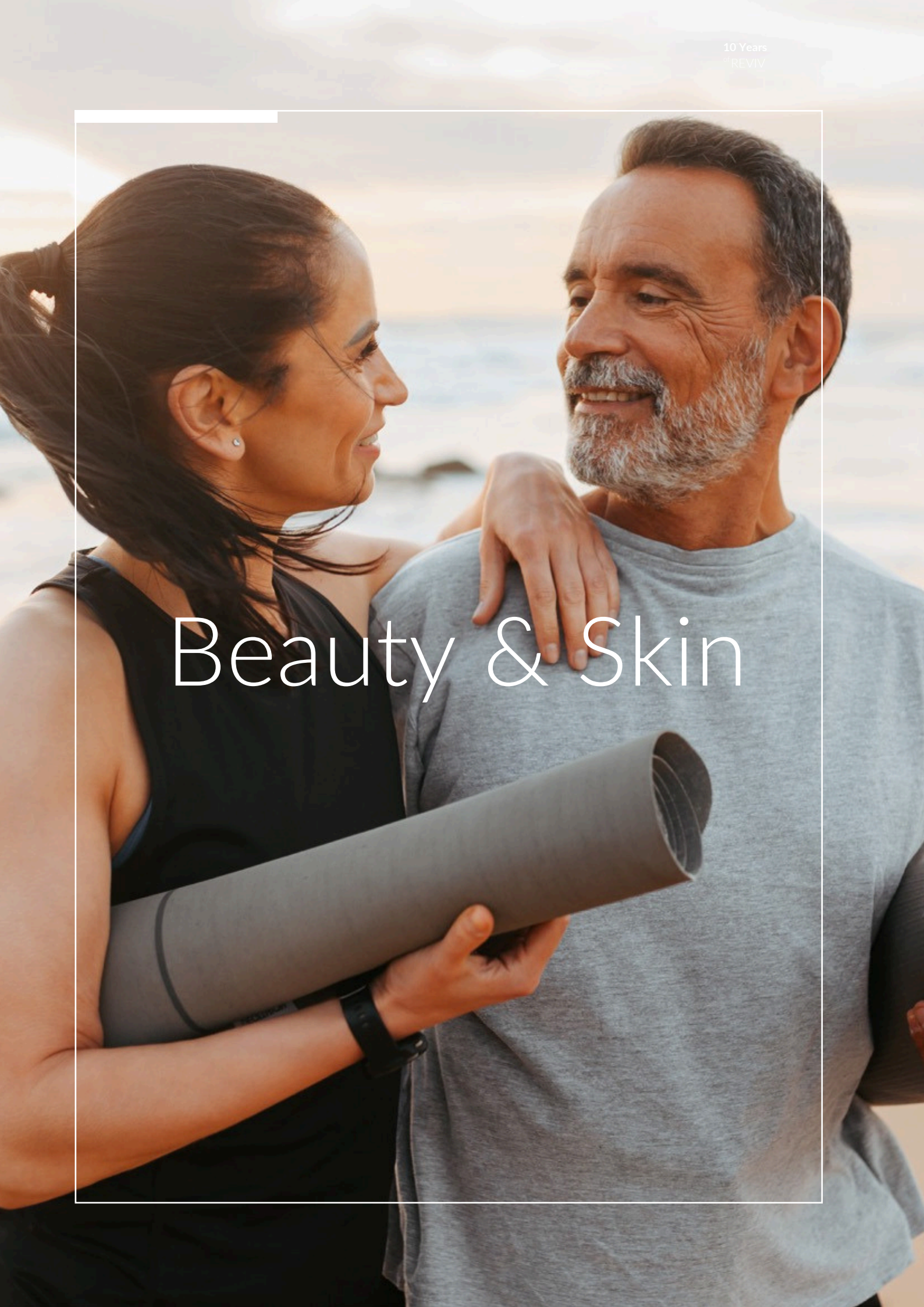
Fatigue Assessment Scale Scoring pre-IM or IV therapy

Fatigue Assessment Scale Scoring 48 hours after IM or IV therapy

75% **had improvements in their energy scoring** following 1 therapy

25% **had complete resolution of symptoms** following 1 therapy

0% had no significant worsening of their scores



Beauty & Skin

Beauty & Skin

Case Studies

"Looking good helps you feel good. Improving the appearance and health of the skin or hair is a common reason people use IV drip therapy in their beauty routines. LIquivida's scientific team have been exploring this for many years, across several conditions affecting the skin."

Dr Michael Barnish

- Hyperpigmentation Case Study
- Eczema Case Study
- Rosacea Case Study
- Acne Case Study

Response of a Multi-Nutrient Intravenous Infusion on Hyperpigmentation and Skin Quality

Dr Michael J.A. Barnish MBChB
Clinical Case Studies Liquivida Global Ltd.

Abstract

Hyperpigmentation is a common condition affecting all ethnicities, in particular those with darker skin tones. Current treatment interventions are topical hydroquinone and oral tranexamic acid. Due to their potential interaction with melanin production, glutathione, vitamin C have been studied as potential interventions for this condition and also as a cosmetic skin lightening therapy. Whether these are successful interventions on their own is inconclusive. This case study explores combined glutathione and vitamin C, intravenous injection and observes the skin, following an eight-week protocol. Although firm findings cannot be ascertained from this study, a perceived effect is noted, with no reported adverse events, and further study would be required.

Introduction

Melanocytes, in the skin's basal epidermal layer, produce melanin, the pigment responsible for producing skin colour and providing photoprotective protection to the skin.1 Melanogenesis occurs in organelles, within the melanocytes, called melanosomes where dopaquinone is formed when tyrosinase oxidises tyrosine as the first step to forming both eumelanin (brown) and pheomelanin (red) pigments.2 Melanin production, induced by the sun's ultraviolet (UV) results in the production of reactive oxygen species (ROS).1

Hyperpigmentation, or melasma, of the skin, is a local and acquired hypermelanosis of the skin. It a common condition affecting all ethnicities, however epidemiological studies report higher prevalence in higher pigmented phenotypes.3 The aetiology of this condition is still not fully determined.4 Hyperpigmentation often appear as brown maclules of the face, often affecting quality of life, even in individuals with a small area of pigmentation.5 Hypermelanosis is not fully understood, however it could occur following excessive inflammation to the skin, or from an inability to successfully clear ROS's, built up from melanin production.1

Gold standard treatment of hyperpigmentation has been topical hydroquinone, but this has been superseded by tranexamic acid (TA), in recent years, following clinical trials that have revealed its effectiveness and safety for treating the condition.5

Glutathione and vitamin C both play a role in melanin production, in different ways and therefore could provide a potential intervention for treating this condition. Glutathione is thought to play a potential role in changing skin colour because in its reduced form it is essential for pheomelanin formation, mediating the switch from eumelanin production to pheomelanin production.6 Reduced glutathione (GSH) is also thought to bind to the copper containing active site of tyrosinase, therefore proposing that glutathione could also inhibit melanin production, via this method.6 Despite these potential mechanisms of action, glutathione's efficacy for skin lightening skin colour or for improving hyperpigmentation conditions is not proven. A randomized control trial of 60 women, from Bangkok, measuring oral glutathione supplementation on melanin index found no statistically significant difference between

those taking it and the placebo group.7 An alternative method of measuring skin colour may have found a different result. There were no serious adverse events throughout this study, involving 250mg oral supplementation. Oral supplementation of glutathione may not be an efficacious route for administration of glutathione as it can be easily degraded by the intestinal enzyme gamma-glutamyl transpeptidase (GGT), making cellular bioavailability potentially challenging and may have accounted for the result.8 In general, glutathione supplementation has been observed in several clinical trials, with no serious adverse events being recorded.7

Sonthalia et al, in 2018, argue the safety and efficacy of glutathione use parenterally for cosmetic use around cosmetic skin whitening treatments, suggesting evidence for these, in particular parenteral glutathione, was limited to one study of poor design and concluded that there was little convincing evidence in favour of glutathione use for hyperpigmentation, calling for more evidence to explore glutathione's efficacy and safety for this condition.9 The authors appear to have a clear bias tone against intravenous glutathione use, focusing on the negative aspects of the one study that they explored for this IV intervention. They reported that this study did not show an effective or lasting treatment for skin tone lightening.9 However, the authors explore the studies faults and limitations in detail. This negative outcome could therefore be down to poor study design and not representative of a true outcome. The authors do not suggest this.

Wantanabe et al share the results of a randomized control trial assessing the effect of topical glutathione on melanin index value, moisture content, smoothness, wrinkle formation and elasticity of the skin. Their findings revealed a significantly lower skin melanin index in the 30 women, as well as significant increases in moisture content, suppression of wrinkle formation and improvement in skin smoothness. None of the case subjects reported adverse events, hinting at its safe use.10

Vitamin C, a potent antioxidant exerts several roles supporting skin physiology, including collagen synthesis and photoprotection.11 It is currently a controversial topic, that vitamin C can inhibit melanogenesis. Studies have demonstrated its ability to do this, but some have only revealed weak effects, especially in the absence of vitamin E.12 Vitamin C also has antioxidant properties, which helps to counteract the accumulation of ROS species caused from melanin production and UV radiation.11

A study of 17 patients, measuring the efficacy between tranexamic acid vitamin C showed that independently they both improved melasma statistically significantly, however there was no statistically significant difference observed between the two interventions.5

There are several methodologies for measuring interventions for hyperpigmentation in individuals. High resolution cross polarized digital photographs at different profiles can be taken and can be an effective way of observing the result.13 However, there are also several scores that can be determined for measuring a whitening effect. Calculating the individual typology angle (ITA°) using a spectrophotometer, utilizing a white ceramic plate is one methodology for measuring whitening effect in clinical study. Alternatively, many studies measure either melasma area and severity scoring (mMASI) or Taylor hyperpigmentation scale. Individuals in studies are often scored using the Fitzpatrick methodology to assess baseline skin type. Scoring methodologies will be subjectivity and therefore, computed and systematic methodologies are more favourable to reduce the chance of subjectivity with these outcomes.

Case Presentation

The case in this study was a 49-year-old, Caucasian female who presented with post-inflammatory hyperpigmentation, diagnosed at a specialist aesthetic clinic. The case is of Greek heritage. Alongside examination, Mediterranean skin type and chronic excessive sun exposure, without SPF protection, were the two risks that helped to establish diagnosis. The case also complained of dark circles under her eyes and a dull skin tone. The case had not previously received any topical or oral treatment for this condition.

Fig. 1 (below) highlights the hyperpigmentation observed and the main areas of concern for the case. The case had been wearing SPF sun protection on the face for 2 years prior to the study and had a baseline skin care routine that had been long standing for more than 1 year.

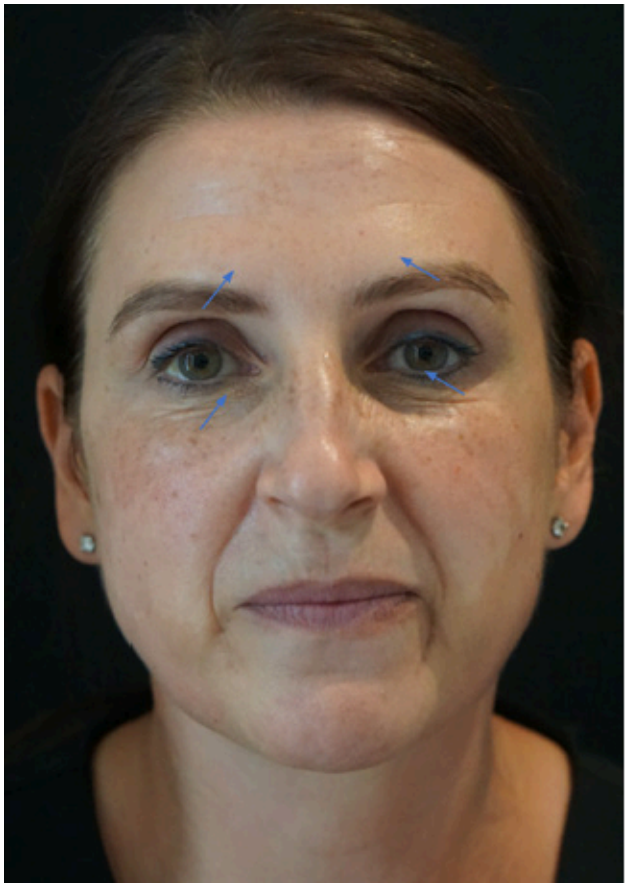


Figure 1. Unedited case photo prior to the treatment displaying significant hyper-pigmentation of the lower face and freckling on the mid face. Arrows demarking main areas of concern.

The case received a weekly, multi-nutrient, intravenous (IV) infusion over the course of an eight-week period, having 8 treatments in total. The multi-nutrient IV infusion contained key ingredients such as glutathione and vitamin C. Rationale for this IV formulation was based upon a full literature review of potentially relevant nutrients for hyperpigmentation. An independent laboratory assessment for pharmacodynamics, particulates and endotoxins was also performed, prior to use.

The case did not change any skin care or SPF habits, keeping them static, as they had been for a long time prior to this study. There were no other treatment interventions, during this study.
Prior to and during the treatment schedule, the case's blood pressure, heart rate, temperature, oxygen saturation and respiratory rate fell within normal limits. The case reported no side effects from the treatments throughout the study.

High resolution, cross polarized photography was not available for this case experiment and the method of measuring the intervention was via standard high-resolution photography and patient perceived effect.

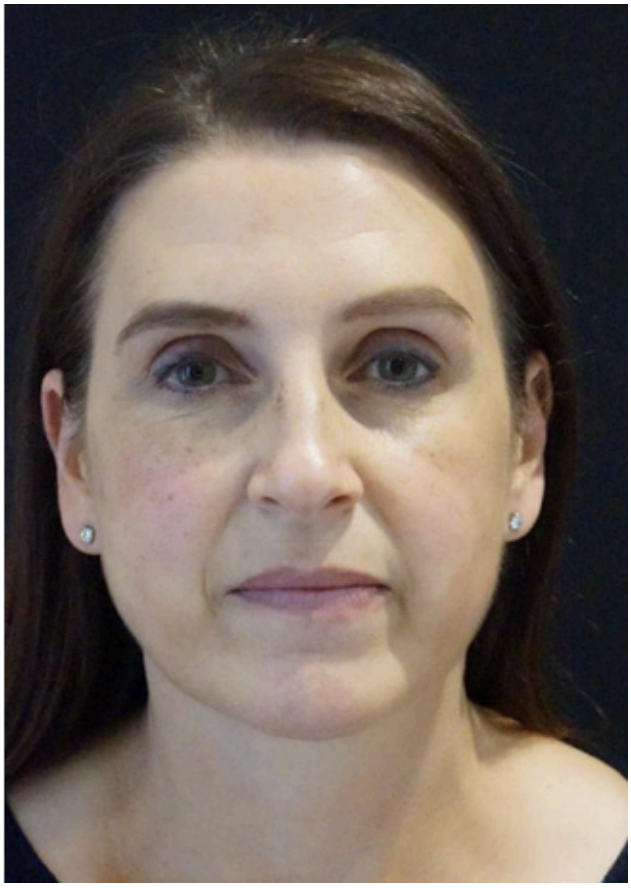


Figure 2: Unedited case photo following the eight-week treatment schedule, displaying a reduction in hyperpigmentation of the lower face and freckling on the mid face with improved under eye skin quality.

The post-treatment image's lighting is slightly different from the pre-treatment image, despite using the same location and camera for the image, at a similar time of day with the window being covered by a blind. However, the image does highlight several improvements. Firstly, the skin tone is more even. The hyperpigmentation is still present around the lower face, bilaterally, but it is softer with a less marked difference between the two skin tones on the first image. The lighting may account for some of this difference. Secondly, the under-eye region of this case appears improved with reduction of fine lines and improved tone. The freckles are also improved and more blended with the surrounded skin tone. Finally, fine lines on the upper lip are also reduced.

Figure 3: Comparative photos of the case pre and post treatment schedule.

Following the treatment schedule, the case reported a significant improvement in the skin's tone and quality and was content with her perceived reduction of the hyperpigmentation.

Discussion

The current literature suggests that glutathione and vitamin C may be helpful stand alone or adjunctive interventions for improving conditions involving hypermelanosis. To date there has been only small scale clinical trials to look into this with only marginal evidence of its efficacy.

Combining these two interventions, in different forms (NAC & glutathione, for example) and providing them to the case in larger, intravenous doses, was tested during this case study, with perceived improved outcomes. With the lack of standardised calculations of skin colour or advanced photographic methods for recording findings, this case is limited in its ability to make a firm judgment, however the perceived result is apparent, following the intervention. It would be appropriate to explore the same experiment considering cross polarized photography, mMASI scoring, skin melanin index scoring and spectrophotometer use, to measure pigmentation outcomes. Additionally skin moisture, wrinkle definition, skin smoothness and firmness could be quantified via several specialist sensors or devices, manufactured for theses purposes. Testing the safety of this multi-nutrient infusion by monitoring renal and liver function throughout the experiment would also be beneficial when intravenous glutathione is used. Comparing these interventions with placebos will also be beneficial to establish potential efficacy of this intervention.

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Eczema. Skin Health.

Demographic Information

Gender:	Ethnicity:	Age:
Female	**Caucasian**	**22**

Customer testimonial:

I have had eczema for 3 ½ years now. My eczema mostly affects my legs and arms, but it has also been across my belly, my back, on my scalp and on my chest, even around my ears.

It got so bad that I couldn't always go into work and I work at a desk in an office. I lived in bandages, my fiancé had to dress me and I barely slept.

My skin was raw. I could barely move. Wearing clothes and having bedsheets touch me was painful and my skin was constantly weeping. Showering and bathing reduced me to tears as it felt like my skin was burning. I only wanted to leave the house if I had to go to the doctor.

From my first treatment I felt awake and energised and over that first weekend if I had a flare up of eczema, it calmed down quicker than it had done before. I feel like my skin looks normal and I'm not limited to where I can go, what I can do or wear.

I know the eczema may never fully go away but the treatment makes me feels and look like it has! It is definitely something I am going to carry on doing.

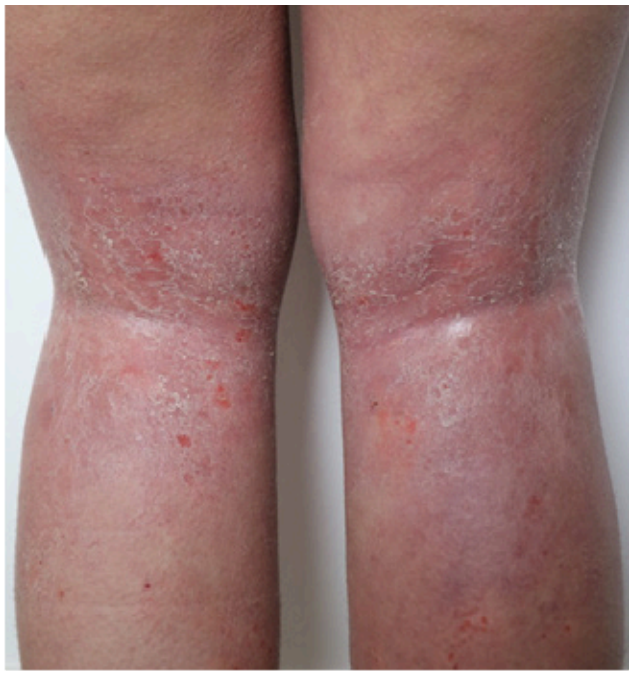
By exploring the customer's medical history, eczema's natural history, her potential triggers, and lifestyle, we were able to establish what her potential nutritional requirements were, that may have been compromising her skin's health and altering the normal, natural skin cycle. In-depth analysis of the existing literature for different nutrients and eczema was undertaken and stratified to an IV formulation. The infusion had undertaken laboratory testing, prior to administration, to ensure safety. The intravenous infusion contained several nutrients, delivered at 2-weekly intervals, for the duration of 12 weeks, representing 2 normal skin cycles. The results show an almost complete resolution of symptoms, something that conventional dermatological management (moisturising creams, steroids and antibiotics) had been unable to offer the patient over her 3 ½ year presentation.

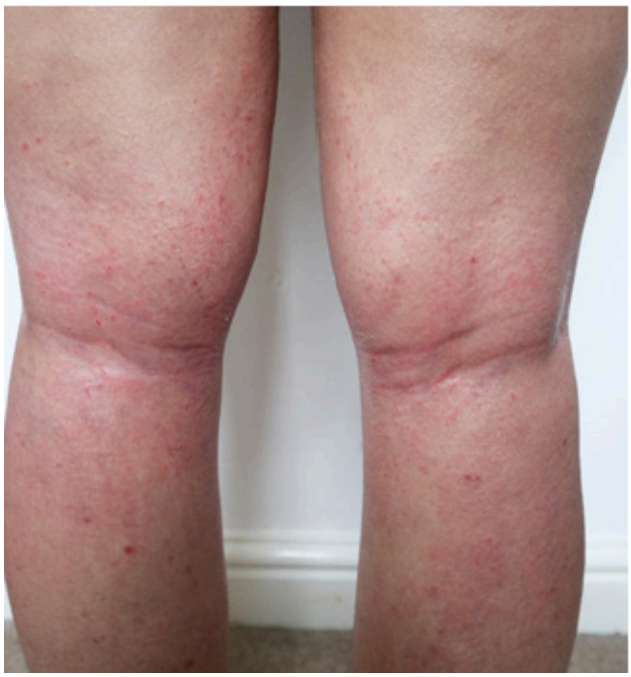
Treatment schedule:

Skin Radiance Infusion + 2x Glutathione Pushes, administered every 2 weeks, for a 12 week period.

Patient photographs:

Before and after photographs of case study following 6x personalized IV nutritional therapies, spanning 12 weeks.





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The Use of Intravenous Glutathione in the Management of Rosacea

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Clinical Case Studies
Liquivida Global Ltd.

Dr Michael J.A. Barnish MBChB
Clinical Case Studies Liquivida
Global Ltd.

Introduction

Oxidative stress is the imbalance of free radical particles and antioxidants throughout the body. Immunological mechanisms in autoimmune disorders have been shown to increase oxidative stress, leading to aggravation of pathophysiology in a variety of conditions, including rosacea. These molecules are highly reactive throughout the body and can damage vital proteins and lipids which can lead to the breakdown of Deoxyribonucleic acid (DNA).

Given that acne rosacea appears to have autoimmune features we can hypothesise that oxidative stress could worsen the condition and propose antioxidant support as a potential solution for the condition. Rosacea is a common skin condition affecting the face. It is categorised by frequent episodes of transient or continuous erythema, caused by swelling to superficial blood vessels and resulting in a localised pyrexia and erythema, sometimes leading to pain. Sebaceous gland hyperplasia can lead to papule and pustule formation. Phymatous changes, from chronic connective tissue regeneration resulting in fibrosis can occur, which may to fibrosis scar tissue development, in severe cases. Sebaceous gland hyperplasia most commonly affects the nose, resulting in it appearing bulbous in nature. Initially rosacea affects the forehead, the bridge of the nose and the cheeks, with periorbital and perioral areas being spared. Rosacea typically presents as a fluctuating pattern, before disease progression leads to continuous symptoms. Symptom intensification, from exacerbating factors and UV light exposure is typical with the condition. Exacerbating factors that can intensify symptoms include emotional triggers, temperature changes and hot food or drink consumption.

The aitiology of rosacea is unknown, however the precipitating factors, listed above, suggest a potential theory for a lack of normal homeostatic control of the blood vessels that supply the pilosebaceous follicles. Speculative associations with the mite, demodex folliculorim, found in large numbers on the face, is also a prominent theory of aitiology.

Recent research has shown there could be a potential genetic link to the condition. Further studies have discussed genetic variant relationships with almost half of cases with rosacea. These variants are associated with autoimmune diseases, in general, proposing a potential autoimmune link to the condition. Treatment of rosacea depends on symptomology, but typically includes topical antibiotic, topical antiparasitic (Ivermetrin) or azelaic acid as a first line treatment, in primary care. Topical retinoids are commonly used by dermatologists for management of symptoms. There is no known cure for the disease. Resistant individuals are commonly prescribed oral antibiotics.

Diagnosing rosacea presents a variety of difficulties as a range of dermatology conditions identify with the same clinical indicators.

Rosacea is often misdiagnosed and studies have shown that incorrect diagnosis and use of medications could induce rosacea. This can lead to incorrect management of the condition, for instance with topical corticosteroids. The incorrect use of potent topical steroids was found to worsen the effects of rosacea. Treatment for steroid induced rosacea is typically oral antibiotics as first line treatment. Notably, it is also worth considering topical steroid withdrawal syndrome when there is a history of inappropriate use of topical steroids for a significant period of time in patients with rosacea.

With oxidative stress and autoimmunity both considered in the cause or exacerbation of rosacea, Wozniacka et al explored the antioxidant properties of nicotinaminde adenosine dinucleotide (NAD) as a potential treatment for the condition.

They found the topical application of NAD flattened papules and the reduced in erythema with a 75% success rate. This pilot study provides some evidence that antioxidant therapy may have a role in the management of rosacea. However, it is important to note that NAD has 100s of roles in cellular metabolism, so the mechanism of action, for this noted improvement, cannot be firmly concluded to be through its antioxidant effects. Further to this, Dalloglio et al 2020 found applying topical glutathione to participants with rosacea reduced the number and size of lesions on their skin. Glutathione is one of the body's principal antioxidants.

Case Results

Glutathione is a major antioxidant, found in almost all cells of the body. It can neutralise free radical and reactive oxygen species, that can accumulate and lead to oxidative stress. Glutathione is also a cofactor for antioxidant enzymes and is a key component in the regeneration of other antioxidants, such as vitamins C and E. As a cleaner the case had higher than normal exposure to exogenous chemicals and could mean that there was more oxidative stress present and therefore, a higher demand for antioxidants.

We explored a multi-antioxidant intravenous infusion, containing glutathione, vitamin C and N-acetyl cysteine to monitor its effectiveness for reducing the symptoms of rosacea in the case. The proposed antioxidant intravenous infusion underwent laboratory analysis for pH, osmolarity, specific gravity, endotoxin formation and particulate formation to assess for agreeable pharmacodynamic properties prior to utilising this infusion. All parameters were acceptable. See Appendix 1: Certificate of Analysis. The case did not want to explore the topical or oral antibiotic therapy, outlined by national guidance, and wanted to explore intravenous nutrition prior to further review for her symptoms with her general practitioner (GP). Prior to this she had been given topical steroids, which she used and symptoms exacerbated, and therefore was reluctant to re-engage with her GP, despite advice from us. Due to the steroid exacerbation she wanted to avoid medication.

A clear discussion was undertaken with the case explaining the rationale, safety and existing evidence, alongside potential benefits of the intervention, when compared to conventional treatment. The case did not want to explore topical or oral antibiotic therapy, due to concerns of long-term antibiotic use. Prior to presentation the case received topical steroids, which she used for a long period of time and had exacerbated her symptoms.

The intervention was carried out in a specialist intravenous (IV) nutrition clinic, LIQUIVIDA registered with the Care Quality Commission (CQC) and prescribed by a qualified and registered medical prescriber and administered by a registered medical professional.

Case Background

41-year-old caucasian woman who presented with a two-year history of intermittent facial maculopapular erythema with papules and pustules present. This was present bilaterally, on the cheeks and there was peri-oral and peri-orbital sparing. There was notable xerosis over the erythematous region. There was also some involvement on the chin. See Fig 1.

The erythema was positive for itching and burning type sensations, particularly aggravated if there was exposure to UV light. Skin care could not be tolerated and exacerbated the condition. There was no sign of infection. There was no ocular involvement. Systemically she was otherwise well with no symptoms. Her menstrual cycle was normal and regular. Sleep was affected by the burning and itching symptoms, particularly in warmer weather. The case cannot recollect an initial causal event, two years ago, and had no past medical history. She reported taking no regular medication, but supplements daily with oral vitamin D, vitamin C and magnesium. Her general practitioner, in Poland, initially prescribed topical steroid (Mometasone 0.1% cream), which the patient used regularly with some initial improvement. However, the condition persisted, and symptoms returned with more severity, following the course of steroids. There was no further medical intervention and her symptoms have intermittently occurred with no predictability, including no menstrual pattern. The current exacerbation of the rosacea was continuous and had been present for almost one year.

A diagnosis of rosacea was made based on clinical examination and the nature of symptoms and exacerbating factors. For this paper, it is important to bear this in mind as the patient had incorrectly been administering topical steroids. The patient was made aware that oral antibiotics would have been the first line treatment, for her particular

presentation. However, she wanted to avoid regular antibiotic use, for the preservation of her microbiome.

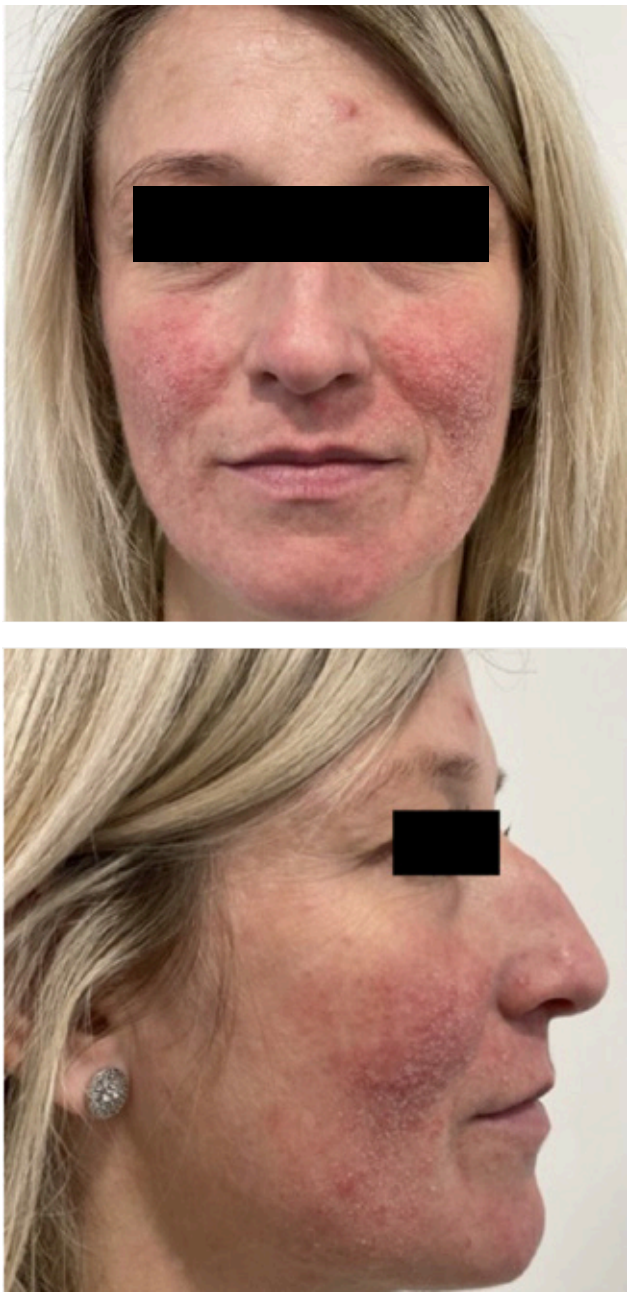

Figure 1 : Case photos (front & lateral) prior to the intervention.

The case cannot recollect an initial causal event, two years ago, and had no past medical history. She reported taking no regular medication, but supplements daily with oral vitamin D, vitamin C and magnesium. Her general practitioner, in Poland, initially prescribed topical steroid (Mometasone 0.1% cream), which the patient used regularly with some initial improvement. However, the condition persisted, and symptoms returned with more severity, following the course of steroids. There was no further medical intervention and her symptoms have intermittently occurred with no predictability, including no menstrual pattern. The current exacerbation of the rosacea was continuous and had been present for almost one year.

A diagnosis of rosacea was made based on clinical examination and the nature of symptoms and exacerbating factors. For this paper, it is important to bear this in mind as the patient had incorrectly been administering topical steroids. The patient was made aware that oral antibiotics would have been the first line treatment, for her particular presentation. However, she wanted to avoid regular antibiotic use, for the preservation of her microbiome. The case had been practising a vegan diet for six and a half years, avoiding animal proteins and products. She received occasional vitamin B12 injections because of this and had no symptoms of vitamin B12 deficiency. The case also reported that she ate one meal a day on average and consumed limited coffee. The case's occupation, as a cleaner resulted in daily exposure to multiple cleaning products that potentially harboured harmful chemicals. The exposure to these chemicals remained largely static throughout the study, with a change to the window cleaning product only to a vinegar-free product. The remaining exposure stayed the same.

Intervention

The case received six multi-nutrient intravenous infusions. The frequency of these infusions was once weekly.

The case was asked to not alter any aspect of her life, including diet and continued not to use skin care Supplementation was continued, as before as had been on these supplements for several years. Outcome measures were observed through standard clinical photography and patient feedback questionnaire. Photographs were taken using mobile photography.

Safety outcomes were measured by obtaining the following blood biomarkers:

- Urea & electrolytes (renal function)
- C-reactive protein (CRP) (inflammatory marker)

These bloods were obtained prior to the intervention and repeated one week after the final infusion.

A superior technique for clinical photography would be high resolution cross polarized photography, however this was not available during the time of intervention.

Outcomes

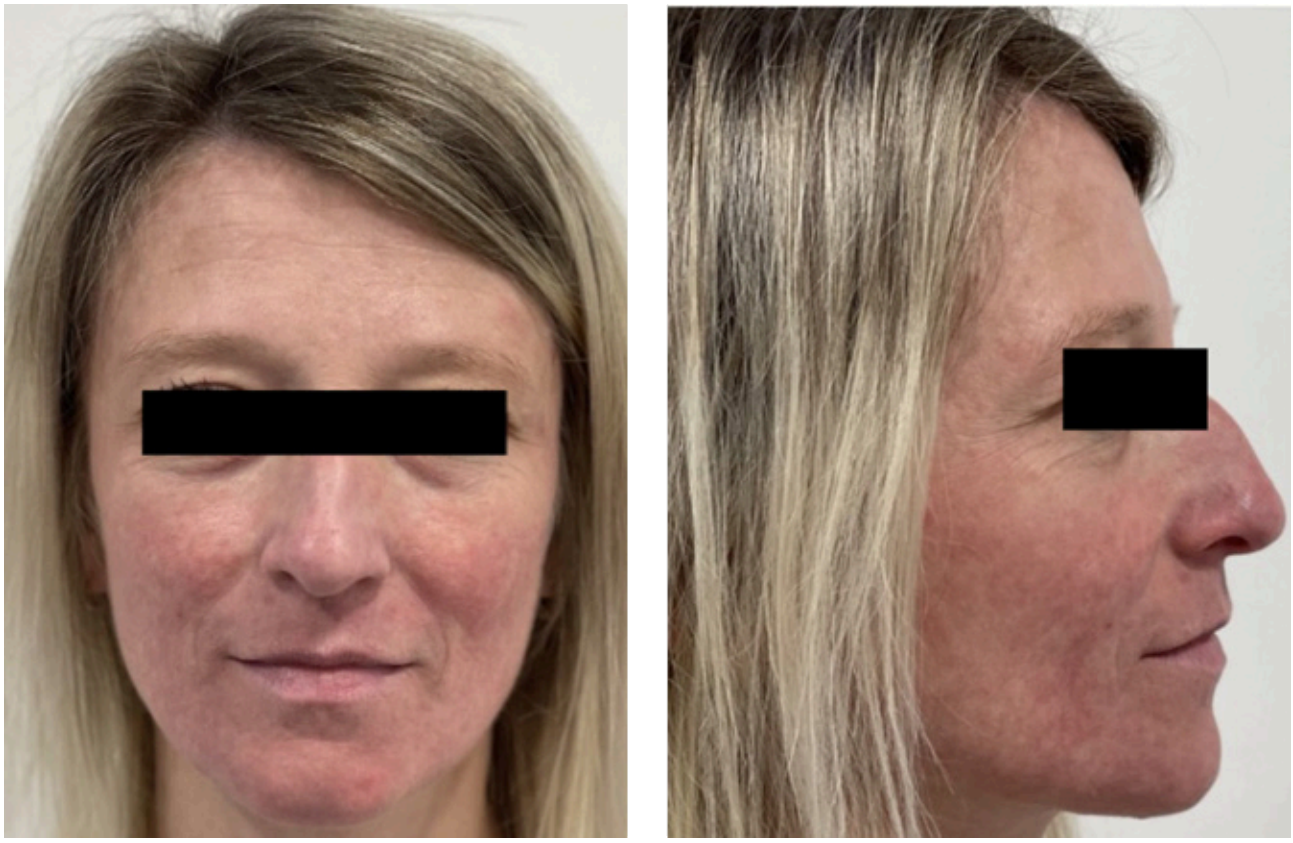

Figure 2: Case photo following intervention. 7 weeks after the initial photography.

As demonstrated in figure 2 highlights the results following the intervention, showing improved symptoms of rosacea and appearance of healthier looking skin. There is a marked reduction in erythema and improved skin texture and tone.

The xerosis has vastly improved overall. Upon further examination there is minimal dry skin towards the upper right side of the cases lips. Papules and pustules appear visibly reduced in number and size, bilaterally. Some erythema still persists, particularly on the nose region.

Measurable outcomes were conducted using patient surveys upon each visit. Symptoms such as burning, itching, redness, sleep, hair quality and energy levels were given a subjective score from 0 to 10.

- For burning, itching and redness a score of 10 represented the most severe score and a score of 0 represented no symptom present.
- For sleep quality, hair quality and energy levels, the score of 10 represented optimal hair quality, sleep quality or energy levels and a score of 0 represented the highest severity.

Each symptom was analysed on the cases weekly visit to the clinic, prior to each intervention and reported by the patient. The patient was also asked to report any other perceived benefits as well as adverse events. Figures 5 and 6 reveal the results of these outcomes.

From these scores there is a clear reduction in symptoms prior to the third infusion. There is an exacerbation of all symptoms prior to the fourth infusion and was potentially due to a period of sunny weather. Following that week, and despite the weather being summer weather for the following weeks, the symptoms continued to fall until they were no longer present by the 7th week.

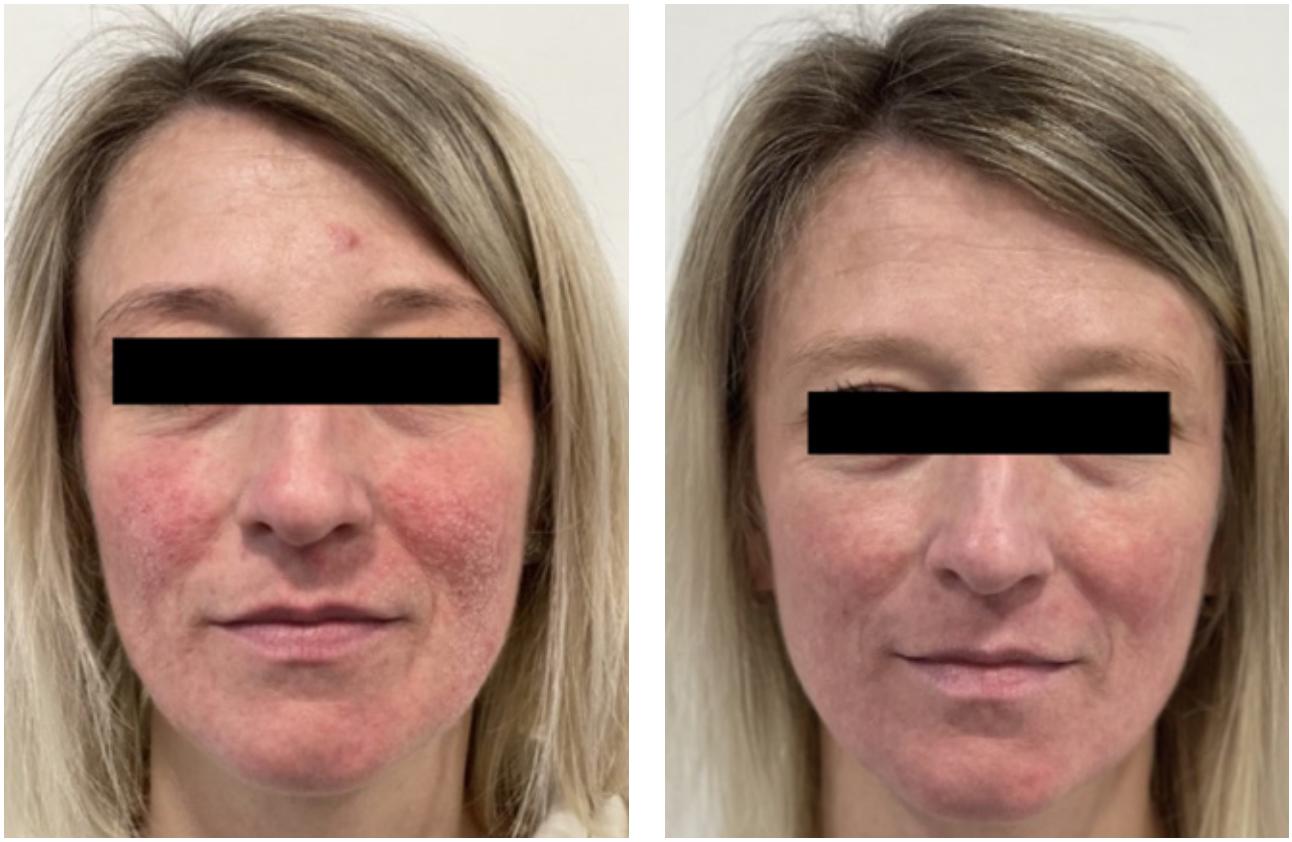

Figure 3: Visual comparisons of pre-therapy (left) and post-therapy (right) frontal face assessing the effectiveness of the intervention.

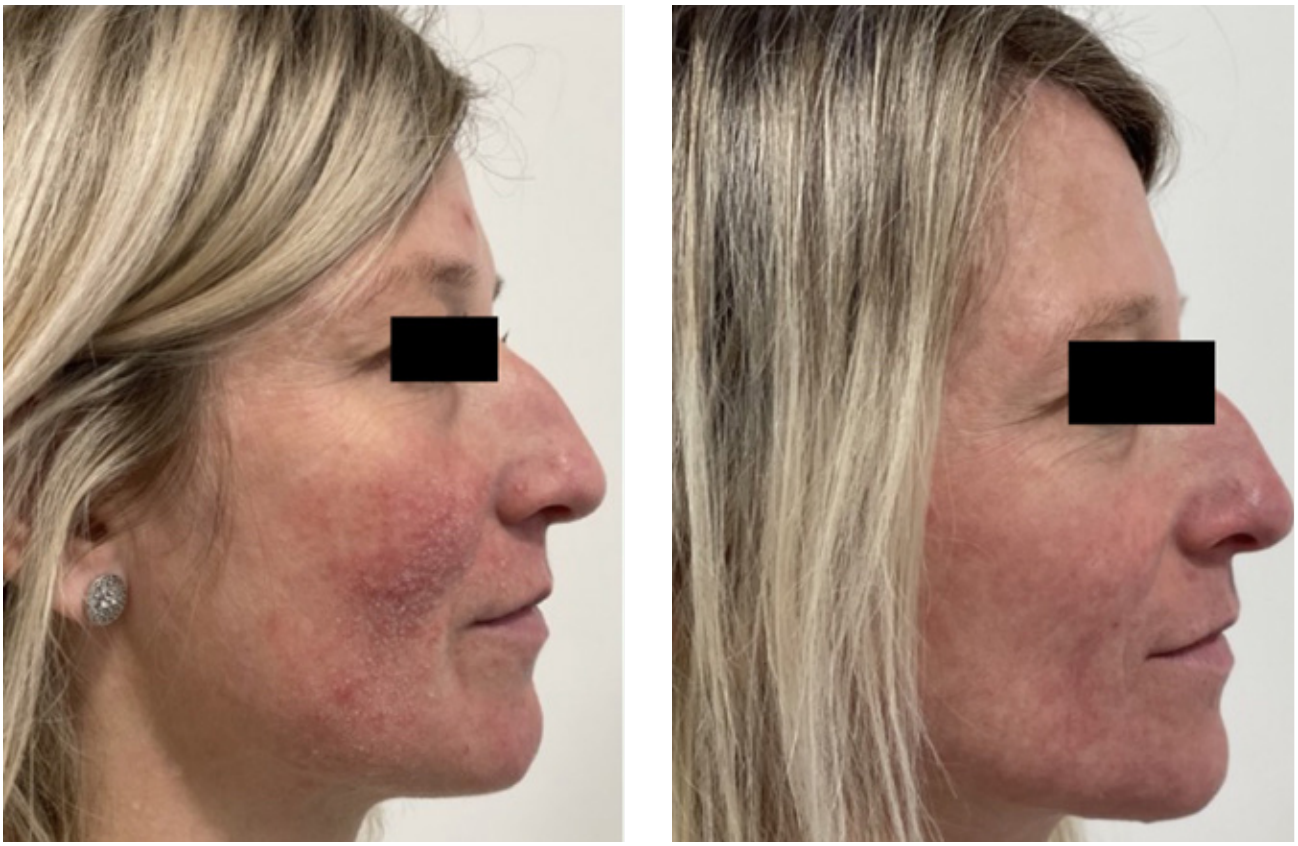

Figure 4: Visual comparisons of pre-therapy (left) and post-therapy (right) lateral face assessing the effectiveness of the intervention.

Symptom	Pre-trial	Post-trial
Burning	3/10in cold weather 10/10 in warm weather	0
Itching	5/10	0
Redness	5/10	0

Figure5:Severity of symptom scores throughout the interventionhighlightingareductioninperceived symptoms bythe patient for erythema (redness), itching and burning sensation.

Lifestyle	Pre-trial	Post-trial
Sleep quality	1/10	10/10
Energy levels	4/10	10/10
Hair quality	10/10	10/10

Figure 6: Severity of symptom scores throughout the intervention highlighting an improvement in perceived symptoms by the patient for hair quality, sleep quality and energy levels.

As demonstrated in figure 6, hair quality was noted to be significantly improved, as was sleep quality. Energy levels were also improved. These factors show how the intervention improved the quality of life of the case, alongside rosacea symptom resolution.

Another perceived benefit, reported by the case, but not formally assessed were noticeable improvements in finger and toe nail quality, strength and growth rate.

No adverse events or negative experiences were noted by the case or observed in clinic during any or following the treatment schedule.

Safety of the intervention was also assessed through blood biomarker analysis. As demonstrated in figure 7, Biomarkers included urea, creatinine and high sensitivity C-reactive protein (HsCRP).

Blood	Pre-trial	Post-trial
Sodium	139	136 4.5
Potassium	4.7	99 26 3
Chlorine	101	50 0.3
Bicarbonate	28	
Urea	3.7	
Creatine	44	
CRP	8.8	

Figure 7: Table outlining the biomarkers prior and after the intervention. Initial results reveal a high HsCRP and normal urea and creatine.

The results demonstrate that the treatment schedule did not alter renal function and there was a significant fall of HsCRP into optimal ranges. The HsCRP has been raised prior to the intervention.

Upon discovery of the initial raised HsCRP, the case was clinically assessed and examined, with the absence of any other inflammatory signs or symptoms prior to the intervention. Therefore, it was thought to be linked to the exacerbation of rosacea. The fall in HsCRP and preservation of renal function, alongside the absence of adverse events and experiences gives reassurance on the safety of the intervention in this case.

The management of rosacea with multi-nutrient intravenous therapy.
Further research is required to explore the clinical effectiveness of multi-nutrient intravenous therapies for rosacea in other cases with the disease. This can further be investigated assessing responses in different cohorts, both phenotypic and genotypic, with the disease.

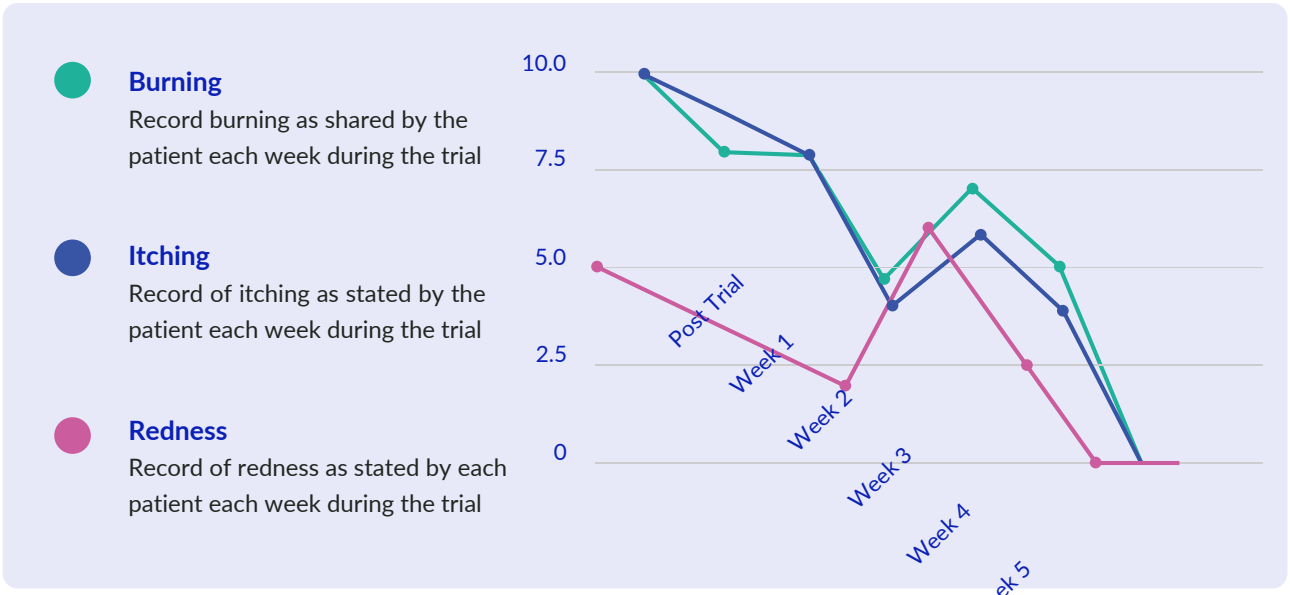

Figure 8: Graph demonstrating the decrease in HsCRP throughout the intervention, which was initially raised prior to the intervention.

Discussion

Presentliteratureis scanty when outlining the role of antioxidant therapy in a variety of skin conditions, including rosacea. There is a theoretical rationale for antioxidants to play a positive role in the management of rosacea, through a potential reduction of oxidative stress. Oxidative stress could have a negative impact on the condition, particularly if the disease has autoimmune origins. Occupational exposure to chemicals daily also may add to the case's oxidative burden. Antioxidants such as glutathione, its precursor N-acetyl cysteine and vitamin C help to neutralise free radical toxins and reactive oxygen species that accumulate, essential for oxidative stress processes.

This case demonstrates that intravenous multi-nutrient therapy, with a focus on nutrients that exert antioxidant effects, was significantly effective at reducing symptoms and appearance of rosacea, alongside reducing associated raised inflammatory markers (HsCRP). Although some erythema was present, the patient reported the resolution of the burning sensation and itching that was associated with her rosacea. It also demonstrates that the intervention was safe, anti-inflammatory, with no side effects, in this individual case. The patient was followed up several months following the intervention and reported no return of her symptoms or worsening of the appearance.
The treatment of rosacea, using multi-nutrient intravenous therapy, has been effective in this one case and improved several measurable outcomes, as well as reducing severity of symptoms. Further case studies, cohort studies or randomised controlled trials are required to investigate this relationship further. However, for a disease process with no identifiable cure and management of symptoms requiring potent medication such as antibiotics and steroids.

Further investigations could utilise high resolution cross polarised photography for outcome measures, which provide a more systematic and clearer type of clinical photographyforskin conditions, such as rosacea.

Conclusion

Thiscase demonstrates that intravenous multi-nutrient therapy, with a focus on nutrients that exert antioxidant effects, was significantly effective at reducing symptoms and appearance of rosacea, alongside reducing associated raised inflammatory markers (HsCRP).

There may be a role in the management of rosacea with multi-nutrient intravenous therapy.
Further research is required to explore the clinical effectiveness of multi-nutrient intravenous therapies for rosacea in other cases with the disease. This can further be investigated assessing responses in different cohorts, both phenotypic and genotypic, with the disease.

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Health &
Wellness

Health & Wellness

Case Study

Evolving Trends in Elective IV Drip Therapy

Historically, elective IV drip therapy has been utilized for enhancing general wellness, boosting energy levels, supporting fitness, and promoting weight loss or beauty and aesthetics. However, over the past decade, particularly due to the COVID pandemic, there has been a noticeable shift. More individuals are now seeking IV therapy for medical purposes, aiming to alleviate symptoms or improve their existing health conditions.

Our LIQUIVIDA data indicates that thousands of customers in the UK are turning to IV therapy to manage symptoms, while hundreds more are focused on enhancing their health amidst illness and disease. We have observed a growing demand for IV drip therapy across various chronic conditions, including post-COVID syndromes, type 2 diabetes, acne, high cholesterol, and autoimmune diseases such as lupus.

Type 2 Diabetes Case

Long COVID

A Clinical Case Study Demonstrating the Response of a Multi-Nutrient Intravenous Infusion with Intramuscular Injection on Glycated Hemoglobin (HbA1C) Level in a Type Two Diabetic

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Abstract

As type two diabetes mellitus (T2DM) becomes ever more prevalent worldwide, innovative therapeutics are required to advance disease management and tackle this major public health crisis. This case study demonstrates the potential for multinutrient and antioxidant intravenous infusions (IV) and intramuscular injection (IM) protocols in the management of T2DM and its sequelae.

A 47 year old female patient with poorly controlled type two diabetes mellitus received weekly multi-nutrient and antioxidant IV and IM treatment over eight consecutive weeks. Changes in glycated hemoglobin (HbA1c), body weight (BW) and blood pressure (BP) were established as outcome measures. A reduction in HbA1c of 24mmol/mol (baseline measurement of 75 mmol/mol to 51 mmol/mol) over the trial period was achieved. Amelioration in blood pressure readings and weight loss were also observed with no alteration in lifestyle factors.
This case demonstrates a rapid improvement in average blood sugar control with multinutrient intravenous and intramuscular injections, in a patient with poorly controlled T2DM. Although IV therapy of micronutrients and antioxidants is a novel method of administration, if further studies demonstrate significant and maintained improvement in HbA1c, physicians have the potential to reduce morbidity and mortality in a large cohort of patients and should therefore seriously consider expanding their clinical armamentarium for treatment of diabetes mellitus.

Introduction

T2DM has reached epidemic proportions affecting approximately 61 million people in Europe, with the International Diabetes Federation projecting an increase of 13% by 2045. (International Diabetes Federation, 2021). This chronic, non-communicable, largely lifestyle associated disease presents a significant economic burden on a country's health service, with an estimated average cost per patient of 3,086 USD. (International Diabetes Federation, 2021).

The pathophysiology of T2DM is characterised by insulin resistance and progressive loss of pancreatic islet B-cell function. Traditional treatment is based on addressing these issues via the use of pharmacologic agents as well as lifestyle improvements and monitoring for and treating co-morbidities that fall under the metabolic syndrome umbrella. Whilst dietary management is stressed as one of the cornerstones of treatment of T2DM, patients rarely understand, nor follow their prescribed diets. Patients have limited, if any, access to a nutritionist / dietician for ongoing advice and follow up is variable at best. The role of improved nutrition has never been in doubt; however, the importance of micronutrient and antioxidant deficiencies are only recently gaining recognition in their possible role in both the pathology and treatment of diabetes.

Glutathione has many benefits including antioxidant activity, preventing cancer progression, improving insulin sensitivity, and reducing cell damage in liver disease. (Galan, 2020). Glutathione deficiency is show in patients with T2DM due to hyperglycaemia and lack of insulin sensitivity (Lu, 2009). A study from 2018 showed that most patients who suffer with T2DM and especially those with microvascular complications, show glutathione deficiency due to the reduced synthesis of the antioxidant (Lutchmansingh, 2018). Glutathione supplementation not only increases glutathione synthesis within the body but reduces the extent of cellular oxidative stress hence improving insulin sensitivity (Sekhar, 2010).

N-acetyl cysteine (NAC) is a precursor to cysteine; a building block of the amino acid glutathione. Increased exposure to NAC can result in increased glutathione synthesis (Mokhtari, 2016) (Gamage, 2014) which thereby propagates the effects of glutathione to neutralize free radical species within the body and in turn, improve insulin sensitivity, reducing the damaging effects secondary to hyperglycaemia.

Vitamin C, also known as ascorbic acid (AA), is a water-soluble vitamin that, unlike most animals, humans cannot synthesize and therefore must obtain from their diet or from supplementation. Bioavailability of vitamin C is thought to be a limitation of oral vitamin C supplementation as plasma levels are tightly controlled by intestinal absorption. IV administration bypasses this, so that very high concentrations of vitamin C can be achieved in the plasma. AA performs many vital roles within our bodies, playing a large role in immunity and protection of cells and tissues from oxidative damage. Oral supplementation with AA has been shown to significantly increase insulin sensitivity postprandially (Mason, 2018) however there has been conflicting evidence regarding AA supplementation and improvement in HbA1c levels (Mason, 2018) (Eriksson, 1995).
Vitamin B12 is a water-soluble vitamin, that plays an important role in hematopoiesis, neurological function as well as DNA synthesis. Its deficiency is highly prevalent among patients with both type 1 diabetes mellitus and T2DM. (Kibirige, 2013). Supplementation has been shown to reduce elevated methylmalonic acid concentrations as well as hyperhomocysteinaemia, thereby reducing the onset and incidence of diabetic neuropathy. (Kibirige, 2013). Vitamin B12 deficiency secondary to metformin use has been unequivocally demonstrated and Vitamin B12 levels should be monitored and corrected. (Akinlade, 2015) (Kibirige, 2013).

Case Presentation

The case was a 47-year-old female, of east Asian ethnicity, who presented to clinic with ongoing poorly controlled Type 2 Diabetes Mellitus (T2DM), despite a treatment regimen of metformin 1g once daily (od), gliclazide 80mg twice daily and dapagliflozin 10mg od. She did not suffer with any other co-morbidities and had no symptoms or diagnosis of diabetic micro or macrovascular complications. She was not taking any oral vitamin supplements. She was a life-long non-smoker and alcohol consumption was within recommended guidelines. Her diet was not favourable for a patient with T2DM, with meals consisting of a high proportion of refined carbohydrates and saturated fats, as well as processed foods. Exercise was also well below the recommended minimum.

Baseline blood cholesterol, renal function and liver function levels were done prior to presentation by the case's specialist team and were within reported to be within normal range. The case's HbA1c, however, was elevated, reading at 75mmol/mol. This is indicative of poor blood sugar control and highlights that the current treatment regime may not be optimal for the case. At presentation, examination findings were unremarkable, except for an initial high blood pressure measurement of 165/97. The case was also overweight with a BMI of 27.12.
A multi-nutrient intravenous (IV) formulation was administered to the case subject once a week for eight weeks. Rationale for this formulation was based on literature review of the potential effects of each nutrient may play on blood sugar metabolism.

The case study was advised not to change her diet, nor exercise routine throughout the trial. Observations were taken weekly, prior to each IV therapy. HbA1c was measured at week 0 and a further two times, at 6 weeks and week 13.

The case tolerated the infusions and injections well, with no significant adverse events reported and subjective improvement in energy and skin, hair and nail health for the duration of the trial. .

Case Results

Primary outcome

The case's initial HbA1c reading was 71mmol/mol, indicative of poorly controlled blood sugars despite triple therapy. The results demonstrate a significant and rapid improvement in her HbA1c readings, with a 32% reduction from baseline over the course of the trial. The final result of 51mmol/mol places her blood sugar control within the target of an HbA1c level of 53mmol/mol for adults on a drug associated with hypoglycaemia, such as the sulphonylurea or gliclazide. Figure 1 (below) displays the HbA1C fall.

Secondary outcome

Macrovascular complications, secondary to poorly controlled diabetes, include peripheral vascular disease, coronary artery disease and cerebral artery disease.

A decrease in blood pressure was observed throughout the trial, from a baseline measurement of 165/97 to its lowest of 132/74 on the 6th treatment to 138/82 on the final treatment. Even though an element of fluctuation in

Timescale	HbA1c
	75mmol/mol
	.
	61mmol/mol
	.
	51mmol/mol
	.
Baseline (Week 0) Week 6 Week 13	

Figure 1: HbA1C readings of the case throughout the course of the case study.

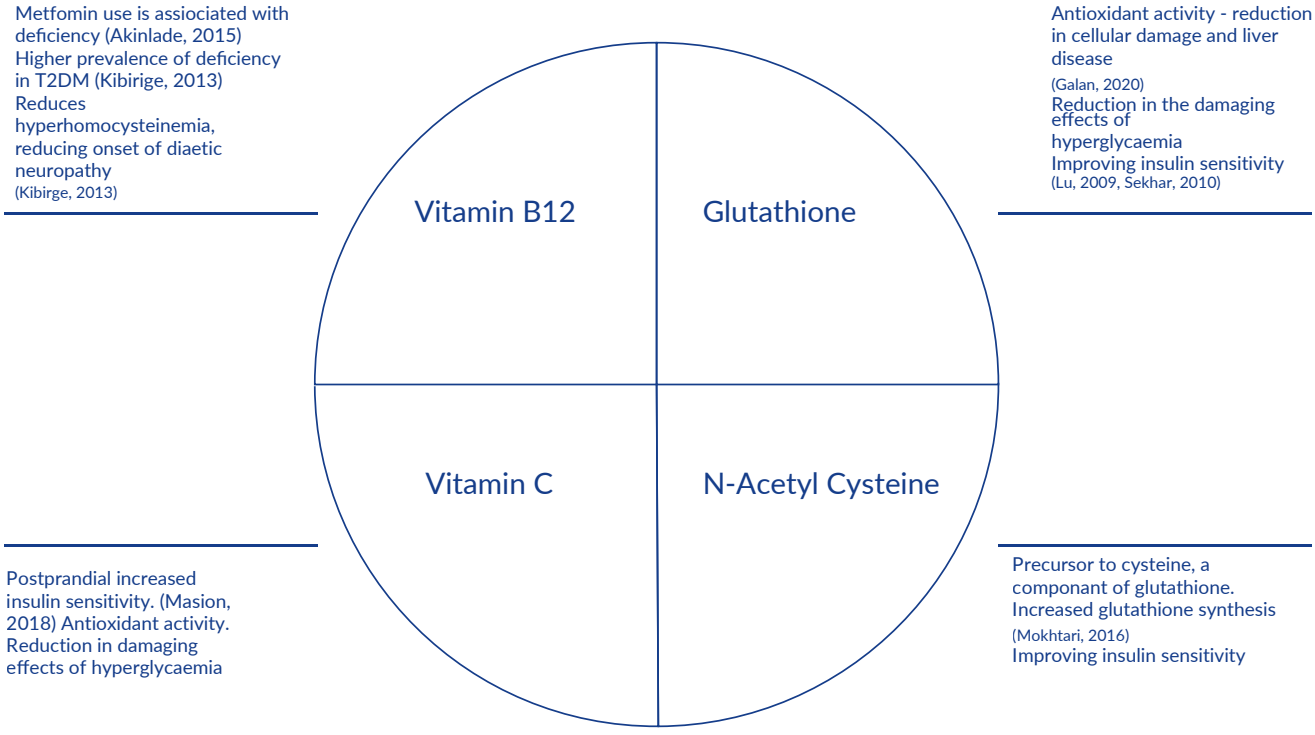
readings is expected, the case's initial reading is consistent with stage 2 hypertension and encouragingly by the end of the trial, her BP had decreased to much nearer the target of 130/80, without the need for anti-hypertensive medication.

Weight loss of 3 kilograms (kg) (24/09/2019: 73kg – 18/11/2019: 70kg) was also observed during the trial, without altering her diet or exercise routine, throughout the course of the eight weeks. Whilst her BMI remained in the overweight category, this is an encouraging finding given how important weight loss is, in particular a reduction in central adiposity, for increasing fasting resting metabolic rates and improve insulin sensitivity in T2DM patients. (Clamp, Hume et. al, 2017).

Discussion

This case study demonstrated a reduction in HbA1c over the trial period where the patient received eight consecutive weeks of IV and IM therapy. As well as an amelioration in HbA1c, an improvement in blood pressure and weight loss were also achieved. Lifestyle factors that would have acted as confounding variables, such as diet and exercise were accounted for, as we asked our patient not to alter any of her daily routine.

Glycated hemoglobin HbA1c was used as the laboratory test to monitor response to treatment. The patient did not suffer from any comorbidities known to decrease the reliability of HbA1c as an indicator of diabetic control which therefore allowed an accurate representation of the mean blood sugar control over the previous 120 days; particularly useful in patients presenting an unrealistically good report of their home glucose tests. Intravenous and intramuscular nutrient therapies aim to optimise the cellular bioavailability, see figure 3 (below). It would be important to establish whether oral administration of these nutrients could establish a similar reduction of HbA1c, to the same extent, at the same rate. Further research is suggested to further investigate the efficacy of multi-nutrient injectable therapies in patients with poorly controlled diabetes. These should be tested both as an adjunct to medical treatment, as well as a solo intervention. With a significant result, such as this and with the burden of diabetes set to be economically and socially challenging, this would be important research to consider.



Limitations

The finalHbA1c reading was taken five weeks post trial completion. This may have resulted in an under-estimation of the true effect of the IVs on HbA1c. To evaluate the hypothesised improvement of HbA1c secondary to IVs more accurately, the post-trial result should have been taken at week 20, not 13.

The trial was carried out over a relatively short timeframe and whilst demonstration of a rapid improvement in HbA1c in a patient with poorly controlled T2DM is very promising, it was not determined whether this improvement was maintained over the subsequent months once treatment had terminated. Further measurements of HbA1c, for example 3, 6 and 12 months after the trial would help establish whether HbA1c returned to pre-trial levels or whether maintenance therapies are required to ensure a plateauing of HbA1c values or indeed whether they continue their downward trend further to pre-diabetic levels.
The case had received multiple frequent IVs as well as IM treatments in the lead up to the trial. These therapies act as a confounding variable that could not be accounted for.

Although there was an improvement in HbA1c, weight and blood pressure, the overall safety of the treatment schedule was not fully assessed, with no follow up liver and renal function testing done throughout or following the study. Further research should measure safety as well as efficacy with regards to administering intravenous nutrient treatments to someone with chronic disease.

Further Research Recommendations

This isanindividualcasestudy.A case series assessing the efficacy of relevant multi-nutrient IVs and IMs on hyperglycaemia in individuals with T2DM should be conducted in different individuals, helping to establish a basis for further study. Randomized control trials would test hypotheses around efficacy of this intervention. Hypotheses regarding delay in onset of diabetic micro and macrovascular complications secondary to the correction of micronutrient and / or antioxidant deficiencies could also be assessed. Safety of this intervention should also be determined, measuring liver and renal function, as well as adverse event reporting, throughout the intervention period, and after. This is particularly important in diabetic patients, that may have pre-existing microvascular complications, leading to chronic renal insufficiency.

A double-blinded randomized control trial could build on this case study to assess whether this intervention significantly reduces HbA1C levels in poorly controlled diabetic patients, compared to a placebo group, receiving just normal saline solution to determine, monitoring safety blood markers, such as renal and liver function tests. Blood pressure and weight are other observations that could be monitored throughout the study. This experiment could be repeated in different ethnic groups and to trial this multi-nutrient therapy as a monotherapy intervention, comparing it to existing therapeutic interventions.

This case highlights a possible novel treatment for the management of poor sugar control in a type II diabetic patient, which further research should explore. The implementation of antioxidant and micronutrient testing as well as their replacement via IV and IM therapies into standard medical practise presents a financial and logistical challenge. At present, neither investigation nor treatment modalities are readily accessible to the general population in developed, let alone developing countries, but with further research and advances in technology, these tests used in combination with establishing nutritional protocols give real hope for T2DM patients and bring us, as physicians, one step closer to enable personalized medicine to become a reality.

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Diabetes

Diabetes

Case Study

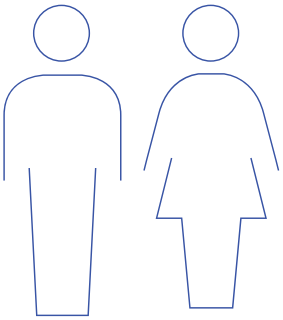
"Monitoring blood glucose control in a cohort of our diabetic customers using IV drip therapy showed that there is potential efficacy its use for supporting management of type 2 diabetes. Type 2 diabetes is a disease of imbalanced nutrition and has a significant global burden, set to increase over the coming decades. Finding new ways to support this condition is important for the global scientific community"

Dr Michael Barnish

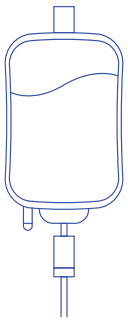
A Stepping Stone to RCT

Expanding on from our previous case study, LIQUIVIDA embarked on further case studies in type 2 diabetes and compiled a case series. The IV formulation was personalized to type 2 diabetes, based on LIQUIVIDA literature review of 170 published peer-reviewed papers.

Outcomes were monitored through measuring HbA1C, a measure of average blood glucose levels and is a widely accepted measurement of blood sugar control in people with type 2 diabetes.



UK customers
Aged 25-65
Male & Female
Mixed ethnicities
Type 2 diabetes



Multinutrient IV formulation, personalized to type 2 diabetes

Baseline & post-study outcome measures collected: type 2 diabetes

- Glycated hemoglobin (HbA1C)
- Fasting glucose
- Renal function
- Liver function
- Blood pressure
- Weight

6 x weekly multi-nutrient intravenous therapy

Day 60 Final Assessment

26%

had significant falls in their HbA1C of more than 5mmol/mol following the therapy

53%

had a fall in HbA1C

6%

had no change to HbA1C levels

10.5mmol/mol largest fall in HbA1C

86%

reported feeling better, with improved wellness outcomes, during the time of IV therapy administration

IV Therapy & the Future

Top Science-Backed Benefits of IV Nutrition

Quick Effect
Delivers nutrients in just 40 mins..

Immune Boost
Zinc+ Vitamin C = stronger defense

Pregnancy Support
Hydration & nausea relief.

Anti-Aging
Delays signs of aging with antioxidants.

Hangover Fix
Rehydrates and eases nausea.

Fast Recovery
Post-surgery or fatigue? IV speeds it up.

Hormone Help
Eases menopause + boosts fertility.

Mood & Stress Relief
Reduces anxiety, uplifts mood.

Headache Helper
Magnesium soothes migraines.

Detox & Cleanse
Flushes out toxins efficiently.

Hangover Fix
Rehydrates and eases nausea.

Glutathione Glow
Liver detox + skin radiance.

IV Therapy & the Future

Case Study

One person's nutrient intake and demand will differ from another's. This will also fluctuate for an individual, on a day-to-day basis, depending on their:

- Genetics
- Environmental exposures
- Experiences
- Choices

"Exploring these determinants allows us to build more personalized protocols for our customers for IV nutritional therapy. We are seeing a rapidly growing demand for personalisation within LIQUIVIDA clinics.

I believe this results in better wellness and health outcomes. Powered by science, we will see the full adoption of this approach by the IV therapy industry, within a decade."

Dr Michael Barnish

Hyperhomocysteinaemia

Response of Moderately Raised Homocysteine Level to Personalized Supplementation of Nutrients via Intravenous Infusion and Intramuscular Injection

Dr Michael J.A. Barnish MBChB
Clinical Case Studies LIQUIVIDA Global Ltd.

Abstract

Moderate hyperhomocysteinemia can be linked to common genetic mutations, including ones within the MTRR and MTHFR gene. Hyperhomocysteinemia has independently been linked to increased risk of atherosclerosis, cardiovascular disease, and cerebrovascular disease.

This case explores a man with the MTRR A66-G G/A genotype and a moderately raised homocysteine level, to determine the response of hyperhomocysteinemia to a multi-nutrient intravenous infusion and intramuscular injection. Following a course of two multi-nutrient treatments, two months apart, a reduction in homocysteine, blood pressure and weight was observed.

This case study outlines a potential for multi-nutrient injectable treatments for the management of moderate hyperhomocysteinemia and its sequalae in those at with a potential genetic risk, such as MTRR A66-G polymorphism.

Introduction

Homocysteine metabolism

Homocysteine is a sulfhydryl-containing amino acid and is formed from methionine, an essential amino acid, following its metabolism.1 Homocysteine is reconverted to methionine, following methylation via two pathways, via betaine homocysteine methyltransferase (BHMT) or methylation from 5-methyltetrahydrofolate (5-MTHFR). 5-MTHFR is an activated form of folate. 2 Figure. 1 outlines the metabolism of homocysteine.

Several nutrients of the B vitamin family are required for the metabolism of homocysteine, with deficiency of these vitamins leading to higher risk of elevated homocysteine levels.2 Vitamin B6, folate and vitamin B12 are all required, with folate and vitamin B12 involved in re-methylating homocysteine to revert back to methionine and vitamin B6 resulting in the irreversible removal of homocysteine,

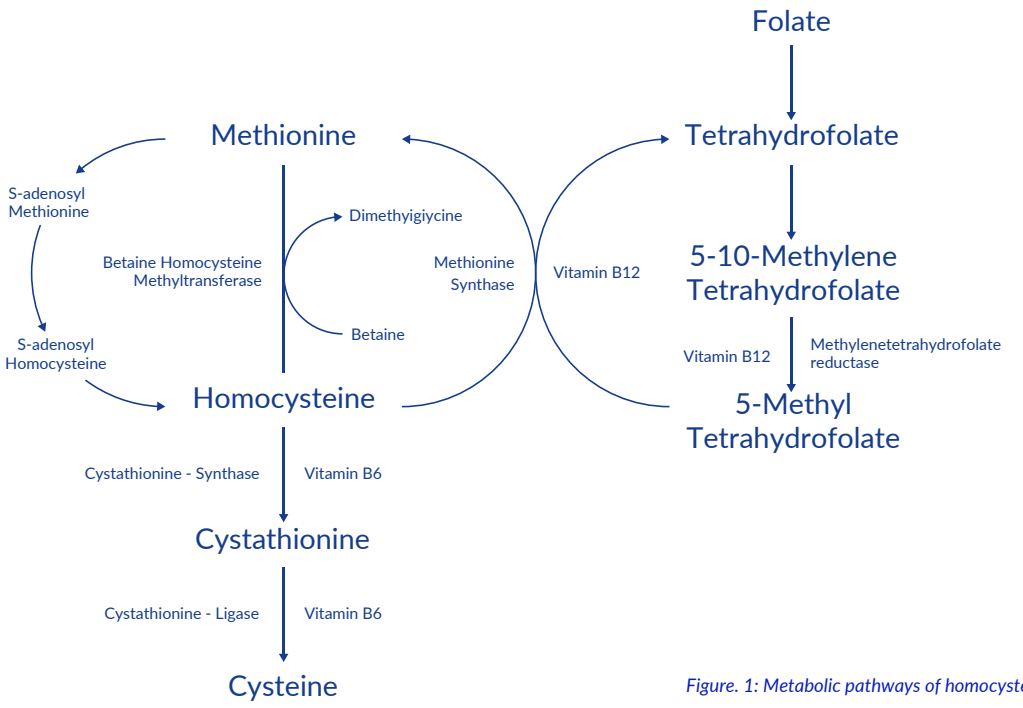


Figure. 1: Metabolic pathways of homocysteine metabolism.2

condensing it with serine to form cystathione and eventually cysteine, a component of glutathione.2

5-MTHFR donates its methyl group to homocysteine, via the methionine synthase (MTR) enzyme that requires the cofactor, methylcobalamin.3 Methylcobalamin is an activated form of cobalamin. Methionine synthase reductase (MTRR) maintains methylcobalamin levels to support MTR's ability to metabolise homocysteine to methionine.4,5 MTRR interacts with cob(II) alamin via reductive methylation to cob(I)alamin, which restores MTR activity if bound to cob(II) alamin.6 MTRR therefore is identified as being a regulatory enzyme in homocysteine metabolism.4

Magnesium and zinc are also co-factors for several of the enzymes involved directly or indirectly with the homocysteine-methionine cycle. Magnesium (Mg^{2+}) is required for optimal activity of methionine adenosyltransferase (MAT), which is responsible for producing S-adenosylmethionine (SAM) from methionine.5 SAM participates in many reactions and is also required to produce methylcobalamin.5

Zinc is required for both the MTR and BHMT pathways of homocysteine metabolism.6 both enzymes are zinc metalloenzymes, containing biological zinc sites that need zinc to function.7

Hyperhomocysteinemia

Previous case control studies and meta-analysis have revealed an association between hyperhomocysteinemia and an increased risk of several diseases, including atherosclerosis, cardiovascular disease, cerebrovascular disease, and dementia.1,8. Experimental hyperhomocysteinemia in humans has resulted in endothelial dysfunction, and in animal models it has been shown to be pro-coagulative, as well as having pro-oxidative and pro-inflammatory effects, resulting in pro-atherogenic gene expression.9

Moderate hyperhomocysteinemia and its link to cardiovascular risk has yet to be firmly determined and nutritional interventions, to reduce the risk of these diseases, in individuals with high homocysteine has not yet been confirmed at a randomized control trial level.2,8

Genetic factors also play a role in homocysteine metabolism. Observational studies of certain, common single nucleotide polymorphisms (SNPs) in the methionine synthase reductase (MTRR) and the methylenetetrahydrofolate reductase (MTHFR) genes are associated with a higher risk of hyperhomocysteinemia.10,11 MTRR is a flavoprotein and maintains sufficient levels of activated cobalamin (methylcobalamin), which is required for the re-methylation of homocysteine back to methionine.12 The common MTRR SNP, rs1801394, resulting in an allele change of A>G at this location results in and amino acid alteration whereby isoleucine is replaced with methionine.13 This substitution is associated with a reduction of MTRR's ability to interact with MTR.4

Although hyperhomocysteinemia is associated with increased risk of cardiovascular disease, associations of the MTRR A66-G SNP and cardiovascular disease remain inconclusive.10

Case Results

Primary outcome

This case describes a 62-year-old caucasian male, who presented in August 2020, with a goal to improve his overall health, reduce weight and prevent hypertensive disease progression.

The case has a past medical history of hemochromatosis, managed by six monthly venesections, essential hypertension and osteoarthritis of the hands and toes. He was diagnosed with essential hypertension in August 2020, just prior to presentation and was commenced on anti-hypertensives, losartan 100mg, and amlodipine 5mg, once daily. He did not take any other regular medicine. He reported a varied diet of predominantly home cooked ingredients with low levels of processed and refined foods and drinks. His exercise behaviour was limited to walking 6500 steps per day because of osteoarthritis. He had never smoked and reported an alcohol intake of above the recommended limits, each week. His father died, aged 65, of a myocardial infarction.

His genetic analysis, performed via microfluidic genotyping, explored the case's genetic information for 71 common single nucleotide polymorphisms (SNPs) that help to identify potential genetic influences on an individual's biology.

Nutritional Genes - Blood

Symbol	rs NCBI	Genotype
MTHFR	rs1801133	C/
MTHFR	ra1801121	C
MTRR	rs1801394	A/
		A
		G/
		A

Figure. 2: Case's genetic results relating to homocysteine metabolism.

Homocysteine	17.40	5.00-7.20	0.00-15.00	umol/L
Folate-Serum	5.00	15.00-25.00	5.50-27.00	ng/ml
Folate-RBC	915.00	906.40-1443.44	634.48-1450.24	umol/L
Vitamin B12	293.00	450.00-800.00	200.00-1100.00	pg/ml
Active B12	49.00	54.00-188.00	37.50-188.00	pmol/L

Figure. 3: Case blood results: November 2020.

The genetic results associated with homocysteine metabolism are shown below in figure. 2.

The results, outlined in figure. 2, reveal that the case's methylenetetrahydrofolate reductase (MTHFR) was likely to have a normal function, across the two most common SNPs within this gene. However, the results do reveal that his methionine synthase reductase (MTRR) has a genotype (G/A) associated with a predisposition to elevated homocysteine levels and increased risk of coronary heart disease.3,4,6,7,8 Homocysteine levels were then checked in November 2020. See figure. 3 (below) to further assess this certain genotype, given the presenting history.

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The results in figure. 3 reveal a higher than normal homocysteine level with a lower than normal serum folate. They reveal a normal level of vitamin B12 and active vitamin B12, falling within the lower percentiles of the normal laboratory range. He had no reported symptoms of vitamin B12 or folate deficiency

Following genetic testing and blood testing, a personalized intravenous (IV) infusion and intramuscular (IM) protocol with potentially relevant nutrients was formulated and underwent pharmacological laboratory testing, to meet safe and acceptable physical properties. This includes testing the infusion for pH, osmolarity, specific gravity, endotoxin formation and particulate formation.

The IV infusion and IM protocol, that was formulated, included nutrients that may be directly involved or indirectly involved with the homocysteine-methionine cycle, or its resultant reactions. The other nutrients that cannot be linked provide antioxidant benefits that may ameliorate endothelial dysfunction, resulting from hyperhomocysteinemia.9

Ascorbic acid was not included in the infusion due to the patient having haemochromatosis, despite its potential antioxidant role.

This same formulation was given to the case twice, with a two-month interval between each treatment, receiving them in February 2021 and April 2021. In January 2021, prior to the nutritional treatment the case stopped his anti-hypertensive medications, against medical advice, as he wanted to manage his health, via a more holistic route.

Vitamin B12	293.00	695.00	450.00-800.00	200.00-1100.00	pg/ml
Folate-Serum	5.00	9.30	15.00-25.00	5.50-27.00	ng/ml
Folate-RBC	915.00	803.00	906.40-1443.44	634.48-1450.24	umol/
Active B12	49.00	179.00	54.00-188.00	37.50-188.00	L
Homocysteine	17.40	10.60	5.00-7.20	0.00-15.00	pmol/ L umol/ L

Figure. 4: Case blood results post treatment in May 2021.

Following the two treatments bloods were repeated in May 2021, 4 weeks after the last treatment. The results are shown in figure. 4 with comparison with previous results (below).

Following both treatments, the case's homocysteine level had improved to within the normal range. Active vitamin B12 levels and total vitamin B12 levels also improved and there was a now normal serum folate level, despite the red blood cell folate level falling to just below a normal limit.

At this stage, there was still no reported symptoms, related to deficiency. Blood pressure readings prior to the initial blood test, and following discontinuation of anti-hypertensives, was 163/98. Blood pressure readings were recorded at 150/84 in July 2021 with no antihypertensive intervention. Weight was also recorded at 93Kg at the first treatment and 90kg at the second treatment. A loss of 3kg was observed over this two month period.

The COVID-19 pandemic had meant that the patient did not receive a venesection for hemochromatosis throughout the period of this study.

To monitor the safety of this treatment schedule, the patient also had his liver function and renal function monitored at the same time as each blood test in November 2020 and May 2021. See figure. 5 below.

Alk Phos AST AST	74.00	86.00	70.00-100.00	40.00-129.00	UL
AST: AST AST: AST	17.00	16.00	10.00-26.00	0.00-32.00	IU/L
GGT Protein -	17.00	18.00	10.00-26.00	0.00-33.00	U/L
Total Albumin	1.00	1.12	0.10-0.78	0.00-0.80	Ratio
Globulin - Total	1.00	0.89	0.00-1.00	0.00-1.00	Ratio
Albumin: Globulin	21.00	21.00	10.00-30.00	5.00-61.00	U/L
Bilirubin - Total	74.50	74.50	69.00-74.00	64.00-83.00	g/L
Bilirubin - Direct	47.40	47.40	40.00-50.00	35.00-52.00	g/L
Bilirubin - Indirect	27.10	26.80	24.00-28.00	19.00-35.00	g/L
Sodium Potassium	1.74	1.77	1.40-2.10	0.90-2.50	Ratio
Sodium: Potassium	21.80	19.60	5.13-15.39	3.42-23.94	umol/L
Chloride Urea	8.70	7.00	0.00-3.42	0.00-5.13	Umol/L
Creatinine eCFR	13.10	12.60	1.71-11.97	3.42-18.81	Umol/L
	135.00	137.00	136.00-142.00	136.00-145.00	mmol/L
	4.40	4.40	4.00-4.50	3.50-5.10	mmol/L
	30.68	31.13	30.00-35.00	30.00-35.00	Ratio
	101.00	104.00	100.00-106.00	98.00-107.00	mmol/L
	4.20	4.50	3.57-5.71	2.50-7.14	mmol/L
	81.00	80.00	70.72-97.24	44.20-106.08	umol/L
	89.00	90.00	90.00-200.00	90.00-200.00	mL/min

Figure. 5: Liver and renal function tests to monitor safety of the treatment.

It is clear from the blood results in figure. 5 show that the liver function and renal function remained stable and within normal levels, eluding that the intervention did not compromise further systemic health and therefore there was benefit seen, with low risk to disruption of liver and renal function.

The case had a further injection of the same treatment, a further 2 months after the previous treatment. He has had no further treatments to date.

Discussion

This case showed an improvement in a moderately raised homocysteine level, following injection of a multi-nutrient-based infusion and intramuscular injection, in a male with presumed, existing atherogenic disease (essential hypertension). There was an improvement in blood pressure readings and a 3kg weight loss was observed. It also highlights that this treatment did not alter renal or liver function, suggesting that the intervention was safe.

The case describes a potential genetic risk for higher homocysteine levels, and a subsequent blood test had revealed a moderate hyperhomocysteinemia. The most relevant nutrient injected here is likely to be methylcobalamin, given the MTRR A66-G genotype was G/A and the active and total B12 levels were at the lower end of the normal laboratory ranges. However, the nutrients, riboflavin (vitamin B2)14, zinc, magnesium, and vitamin B6, that were also infused, are required for homocysteine metabolism into methionine or its metabolism into cysteine. Therefore, we cannot conclude that the improvement was either solely because of methylcobalamin and could have solely been a result of improving the levels of any or all these nutrients together. The other ingredients, included in the treatment support reactions that require s-adenyl-methionine or have antioxidant properties. Although it is unknown if these will directly influence homocysteine levels, they could theoretically support the endothelial dysfunction, that results from homocysteinemia, something that requires further scientific review. This positive outcome highlights the potential of multi-nutrient interventions in the management of chronic diseases, as well as their potential in disease prevention. This study explores the potential that an entirely new class of nutrient based pharmaceuticals could play a role in chronic disease prevention, in individuals with raised homocysteine levels. It also highlights those personalized approaches to healthcare may be effective methods for preventing disease.

Science, to date, has provided an insight into a relatively strong relationship between high homocysteine levels and cardiovascular and atherogenic disease, however this association is less clear for moderately high homocysteine levels. Although several statistically significant papers do associate MTRR A66-G to higher risk of hyperhomocysteinemia, it is important to note that the association of this SNP is associated with cardiovascular and atherogenic disease.

Limitations

The improvement seen in this case, although positive, may not be attributed to the infusions directly. The case was observed over a period of several months and in that time, lifestyle factors, such as exercise and diet can fluctuate and will potentially influence the homocysteine level. Upon discussions with the case, the diet remained consistent throughout this period, as did the exercise, due to the osteoarthritic limitation. The case's blood pressure readings do show improvement over the time; however, these can easily fluctuate, and an average blood pressure reading would be more appropriate.

A literature review to further explore the role of relevant nutrition in improving hyperhomocysteinemia should be conducted. Subsequently a case series, assessing the efficacy and safety of single and multi-nutrient intravenous infusions and intramuscular injections on hyperhomocysteinemia in different individuals, exploring response in individuals with the different genotypes for MTRR A66-G, G/G, G/A and A/A. Different routes and forms of vitamin B12, with and without other relevant nutrients could be compared to further explore the relationship of MTRR, homocysteine and this nutrient.

This could be repeated with the other relevant nutrients, to explore their efficacy in supporting homocysteine-methionine metabolism.

Randomised control trial of individuals with moderate or high hyperhomocysteinemia and the same MTRR A66-G genotype could assess efficacy of multi-nutrient infusions and injections in managing the levels. Implementing both genetic testing and homocysteine measurements into standard medical practice is not without its challenges, both financially and logistically. They are not readily assessable to the general population at present, but with further research and technological advancement these tests together could prove promising in establishing nutritional protocols for individual's with atherogenic pathology, secondary to hyperhomocysteinemia.

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Customer Testimonials

"LIQUIVIDA has been **excellent** *since they opened their first location in South Beach. Anytime I feel a little under the weather* ***I feel much better***

"I love IV therapy, it works for me. Great for immune system. Since I started I've never looked back."

"Since having B12 with LIQUIVIDA, I have also visited for vit C and ***recommended the clinic*** *to my wife, who had also had treatments."*

"Service has always been personalized, of a ***high medical standard*** *and well administrated."*

*"The staff are all medically trained and well informed. I **feel well looked after** and cared for and feel assured I'm receiving the best treatments for me."*

*"LIQUIVIDA **is amazing** and always makes me feel better."*

IV Drip Therapy & LIQUIVIDA Customer Feedback

41%

of our customers
The customers of LIQUIVIDA have been surveyed.
for over two years.

68%

of them report using LIQUIVIDA IV therapies for three years or more.

Why our customers booked their The inaugural IV drip therapy.

50%
made up my mind following research

39%
friend or family suggestion

7%
were referred from a medical professional

2%
celebrity endorsement

2%
gifted

IV drip therapy is becoming more widely accepted by the traditional medical communities, with **27%** of our customers reporting that they first heard about LIQUIVIDA through a medical or healthcare professional

Why do our customers choose to supplement nutrients and fluids, intravenously, rather than taking oral versions?

41% of our customers report feeling more benefit with IV supplementation, when compared to oral versions.

49% of our customers choose IV supplementation of nutrients and fluids because they are wanting faster effects.

10% of our customers state that they us IV supplementation state to help them manage an illness or disease.

25% of our customers believe that IV and oral complement each other and supplement via both routes.

6% of our customers don't like taking oral supplements.

8% don't really compare IV and oral supplementation.

IV drip therapy combines both intravenous fluids, alongside intravenous nutrients, such as vitamins, minerals and antioxidants.

86%

of our customers reported that they found the wellness benefits of IV drip therapy to be better than those following oral supplementation

67%

of our customers report using IV drip therapy to deliver both fluids and nutrients intravenously

5%

stated they use IV drip therapy for IV hydration only

28%

stated they use IV drip therapy for the delivery of IV nutrients only

When it comes to their favorite LIQUIVIDA IV drip therapy:

Our customers consistently rank our various IV products as their preferred therapy. Remarkably, **98%** of them agree that their favorite **LIQUIVIDA* significantly enhances their well-being after receiving it. Additionally, **69%** of our customers report that the effects of their favorite IV drip therapy last longer than a week, while **24%** experience benefits that endure for a month or even longer.

58% of our customers reported improved skin

After their preferred LIQUIVIDA IV drip therapy, **33% of our customers reported enhanced hair quality**, showcasing the benefits of our treatment.

84%

of our customers stated that their favorite IV drip therapy improved their energy levels and **43%** of our customers reported improved sleep quality following their favorite IV drip therapy.

51%

also reported that their fitness performance improved, after having their favorite IV drip therapy.

Other benefits reported by our customers:

- Easier workout recovery
- Faster recovery from a viral illness
- Improved mental clarity & mood
- Pain reduction
- Improving symptoms of disease
- Feeling more focused and positive

" As we move into our second decade, it excites me to continue LIQUIVIDA's journey to set the **very best global standards** for the IV drip therapy industry, in safety and efficacy, to ensure we **continue to help** our customers around the world achieve their health goals. Digitally enabled, over the next 10 years we will see a **new age of IV drip therapy,** being safely available to more people around the world. We will see the industry standard change to a deeply personalized or precision approach to IV therapy and see larger clinical trials showcasing its efficacy for both wellness and in the management of symptoms and disease. It's a truly **exciting time ahead** for LIQUIVIDA and the world."

Sarah Lomas, LIQUIVIDA's
CEO