INTRODUCING A BREAKTHROUGH TECHNOLOGY THAT ADDRESSES THE VISIBLE SIGNS OF POSTMENOPAUSAL SKIN AGING

FE:I
BEAUTY TECH

TABLE OF CONTENTS

1 Introduction

2 Negative Effects Of Too Much Iron

- 2 Over 125 Years of Research Reveals Excess Iron's Role in Oxidative Stress
- 4 Collective Knowledge Points to an Unappreciated Contributor to the Visible Signs of Aging

5 De-Ironizing Inducer (DII®): An Innovative Approach to Reducing Visible Signs of Aging

- 6 DII® Technology's Revolutionary Benefits

7 DII® Clinical Trial

- 8 Clinical Trial Results: Eye Cream Incorporating DII® Technology
- 9 Clinical Trial Results: Face Cream Incorporating DII® Technology

10 Key Takeaways

11 About Xi Huang, Ph.D.

12 Endnotes

INTRODUCTION

It's been half a century since the Free Radical Theory of Aging first proposed that free radical reactions are a contributing cause of the aging and death of all living things. In the decades since, dermatologists and cosmetic chemists have tried to use this knowledge to prevent and repair the damage to the skin caused or exacerbated by free radicals triggered by external forces—chiefly UV radiation, air pollutants and irritants from other sources.

The generally accepted solution has been to fight aging by targeting free radicals with antioxidants—such as Retinol, Vitamin E, Vitamin C, Resveratrol and Niacinamide—and the nutrient coenzyme Q10, which all work by neutralizing free radicals and protecting lipids, proteins and DNA (which are extremely sensitive to the oxidation process), as well as the application of sunscreen to prevent or reduce the production of free radicals caused by exposure to ultraviolet rays.

The antioxidant approach that has guided most women's cosmetic skin care regimens is ignoring an opportunity to disrupt the visible signs of aging. Iron accumulates in the upper layers of the skin and is readily oxidized to create damaging free radicals. An innovative, cosmetic non-retinol skin care treatment has been developed to exfoliate excess iron stored on the skin's surface and reduce the opportunity for the formation of free radicals.

This paper will establish the link between increased iron and oxidative damage. In particular, **this paper will outline several peer reviewed studies indicating that increased iron as a result of the cessation of menstruation after menopause is a key contributor to visible signs of aging post-menopause**. This article will describe a novel De-Ironizing Inducer (D.I.I.®) technology that can reduce the opportunity for free radicals to form and cause oxidative damage, as opposed to antioxidants, which can only attempt to neutralize free radicals after the skin has already been exposed. Finally, this article will share the results of a clinical trial of a new eye cream and face cream incorporating D.I.I. technology.

NEGATIVE EFFECTS OF TOO MUCH IRON

Iron—one of the most abundant metals in the human body—is both essential for normal physiological functions and potentially toxic. Controlling iron levels in the body is a critically important part of many aspects of human health and disease-prevention. A critical component of the body's system to regulate iron is ferritin, a protein that can store up to 4,500 atoms of iron per molecule, releasing it when your body needs it. Most excess iron in the body is found stored in ferritin; "free" iron ions are virtu-ally non-existent in the human body.

More than a century of research has built the case that excess iron's ability to produce large amounts of harmful free radicals in the body can create risk factors for a number of diseases.

Over 125 Years of Research Reveals Excess Iron's Role in Oxidative Stress

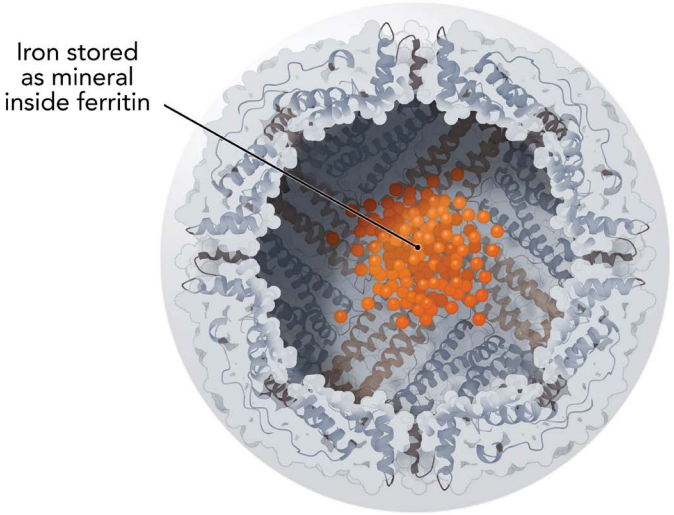
1894	1965	1986	1994	1999	2011
[H.J.H. Fenton]: **Iron promotes the formation of hydroxyl free radicals. Iron causes oxidative damage to proteins, lipids, and DNA in cells and tissues**	[L.R. Weintraub]: **Iron is excreted through skin exfoliation, making skin susceptible to oxidative damage**	[R.G. Stevens] **Increased iron stores increase the risk of risk factors for certain diseases**	[X. Huang]: **Bioavailable iron in mixed coal dusts is identified as an active compound in inducing black lung disease**	[C. Pourzand]: **Ultraviolet A (UVA) causes oxidation by degrading ferritin; UVA-mediated skin photoaging is caused by iron released from ferritin**	[X. Huang]: **Iron and UVA work together to enhance collagenase-1 activity, which leads to wrinkle formation and skin thinning**

The journey to understanding the negative effects of iron in multiple diseases began in 1894, when pioneering chemist Henry John Horstman Fenton published a study describing the interaction between iron and hydrogen peroxide (Fe(II) and H2O2) to yield hydroxyl free radicals—what is now known as the "Fenton reaction."[i] Free radicals are naturally occurring, unstable molecules with extra electrons that seek out and destroy healthy cell functioning.

The next breakthrough toward an understanding of iron's role in skin aging came in 1965 with the publication of Dr. Lewis R. Weintraub's paper "Iron Excretion by The Skin. Selective Localization of Iron in Epithelial Cells."[ii] Following numerous publications reporting the presence of iron in human sweat, he sought to demonstrate the method by which the skin acts as an active excretory organ for iron and its importance in maintaining iron balance. Dr. Weintraub showed that the skin removes iron through the loss of iron-loaded epithelial cells. In defining the quantitative significance of iron loss from the skin, Dr. Weintraub also demonstrated the presence of a great deal of iron in the skin.

In subsequent decades, the observation of increased iron storage in various human diseases encouraged the scientific community to study whether and how iron's role in the Fenton reaction contributed to human diseases by creating hydroxyl free radicals that could damage proteins, lipids and DNA in cells, tissues and organs.

In a hypothesis published in 1981 in the journal *The Lancet*, Jerome L. Sullivan proposed that higher levels of stored iron found in men and postmenopausal women is responsible for a greater incidence of heart disease compared to premenopausal women. In his hypothesis, Sullivan cited observations of heart failure in iron storage diseases, accumulation of stored iron in men as they age and an increase of stored iron in post-menopausal women comparable to levels found in men. While the basis for this sex difference and loss of protection with menopause were unknown at the time, Dr. Sullivan's hypothesis opened the door to important links between iron's role in human disease and the fact that women metabolize iron differently pre- and post-menopause.[iii]



A three-dimensional representation showing ferritin, the iron-storage protein in the body. Ferritin has a spherical shape, and iron (brown) is stored as a mineral inside the sphere.

In a 1984 paper titled "Oxygen toxicity, oxygen radicals, transition metals and disease," published in *The Biochemical Journal*, Barry Halliwell explained the mechanism by which transition metals such as iron are also subject to the Fenton reaction, and described the role played by radicals and metals in multiple disease states, including rheumatoid arthritis and cancer.[iv]

A few years later, Richard G. Stevens was the first to prove a link between increased iron storage and cancer in an epidemiological study published in the April 1986 edition of *The Journal of the National Cancer Institute*. Stevens tested the hypothesis that increased iron storage is associated with cancer risk by reviewing the data of 21,513 Chinese male government workers who had consistent available data going back to 1975 and found that increased iron stores prior to the diagnosis of liver cancer was associated with increased risk of the disease. In his conclusion, Stevens even made a connection between human disease and the Fenton reaction, citing Halliwell's paper to make the suggestion that iron's ability to catalyze the production of free radicals may increase risk factors for certain diseases.[v]

In 1989, Dr. Xi Huang began 30+ years of study on the effect of excess iron on the body, leading to the discovery of his D.I.I. technology. His early research in France as a Ph.D. student explored whether emphysema in coal workers could be related to the production of free radicals generated by inhaled coal dusts. In 1994, he published research identifying iron in the mixed coal dusts as the active compound in producing oxygen free radicals, rather than the fossil free radicals contained in the coal. Subsequently, he demonstrated that the prevalence of black lung in coal workers in the United States correlates with the amount of bioavailable iron in the respective mines across seven coal mine regions. In the following years, Dr. Huang would continue to investigate iron's role in many diseases.[vi]

A 1999 publication by Dr. Charareh Pourzand defined a vital connection between iron accumulated in the skin and damage to skin cells. The ultraviolet A (UVA) radiation component of sunlight had already been shown to be a source of oxidative stress to skin via the generation of free radicals. Dr. Pourzand's publication explained the mechanism by which it happens. While ferritin wasn't mentioned in Dr. Weintraub's article demonstrating the abundance of iron in the skin, by the time of Dr. Pourzand's research, ferritin had been identified as a protein that stores and releases iron when your body needs it. Dr. Pourzand found that UVA causes ferritin to break down and cause an immediate release of ''free'' iron in the cells. The iron is then able to contribute to the creation of damaging hydroxyl free radicals.[vii]

In 2011, Dr. Huang published a paper discussing how iron contributes to skin's accelerated aging in postmenopausal women. Following menopause and the cessation of menstruation (an additional means of removing excess iron from the body), skin bears an increased role in the removal of excess iron.[viii] Dr. Huang investigated how increased iron levels contribute to the manifestation of accelerated skin aging and photoaging after menopause as opposed to estrogen deficiency, which is commonly regarded as the main causative factor. He found that iron and UVA work together to enhance the activity of collagenase-1, an enzyme that breaks down collagen and elastin, leading to skin damage, wrinkle formation and skin thinning.

Collective Knowledge Points to an Unappreciated Contributor to the Visible Signs of Aging

The breakthroughs described above only scratch the surface of decades of research into the implications of excess iron. Among these discoveries are some compel-ling implications for skin, the most remarkable of which may be that increased iron on the upper layer of the skin as a result of menopause—which can be exfoliated–could be as important a determinant of the visible signs of postmenopausal skin aging as estrogen deficiency. Given the scale of the issue—iron levels have been measured to be 42% higher in postmenopausal skin—iron's role in skin aging cannot be ignored.[ix]This understanding upends the long-held belief that estrogen deficiency is the main cause of skin aging in middle-aged women.

> *"increased iron in the upper layer of the skin as a result of menopause could be an important determinant of visible signs of postmenopausal skin aging"*

DE-IRONIZING INDUCER (DII®): AN INNOVATIVE APPROACH TO REDUCING VISIBLE SIGNS OF AGING

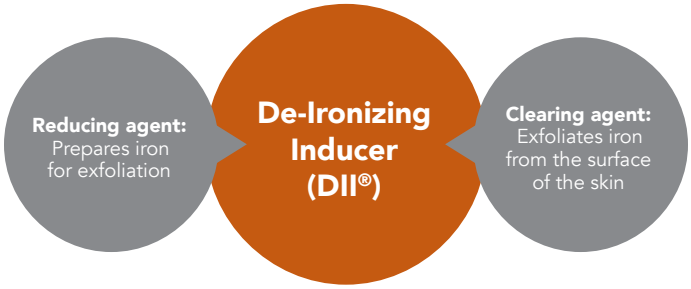
Given what we know about the negative effect of excess iron and the abundant presence of iron in postmenopausal skin, there is a clear need for a cosmetic skin care product that can safely remove excess, excreted iron from the outer layers of the skin without interrupting normal physio-logical functions.

The first step was to zero in on why iron levels increase markedly following menopause. Dr. Huang and his team conducted a series of in vitro and in vivo experiments to explore the relationship between estrogen and iron storage. The results, published in the journal *Endocrinology*, demonstrated that increased iron found in the skin of postmenopausal women is not directly influenced by estrogen deficiency, but rather by the cessation of menstruation.ix This important distinction means that iron found on the skin's surface can be directly targeted for exfoliation to reduce the visible signs of skin aging.

Dr. Huang leveraged his decades of research of the negative effects of too much iron, women's health and advanced chemistry to develop a technology to naturally exfoliate iron from the surface of the skin: De-Ironizing Inducer (D.I.I.). D.I.I. establishes a novel class of skincare products and consists of two core components that work together to extract and clear iron from the surface of the skin before it can contribute to the visible signs of aging.

The first component is the reducing agent, Vitamin C, which has chemical properties that "release" the iron, making it available for exfoliation. This is the most effective and safest way to remove iron from the surface of the skin and reduce the opportunity for the formation of free radicals by reducing the accumulation of iron on the surface of the skin.

The second component is the clearing agent. Once the iron is released from ferritin, it can also continue to exert its harmful effect. To prevent this, a natural calcium carbonate with a high buffering capacity (ability to resist changes in pH) is used to clear the released iron so that it cannot cause damage. This calcium carbonate-buffered system is water insoluble and will resist absorption into the skin to provide protection as long as it is not washed. Dissolution of calcium carbonate releases calcium ions (an essential ion) in the skin and carbon dioxide, leaving no traces of unneeded compounds in the skin. Dr. Huang's unique DII® technology can pack as much calcium carbonate into the formulation as needed.



> *"increased iron found on the surface of the skin of postmenopausal women is not directly caused by estrogen deficiency, but rather by the cessation of menstruation"*

DII® Technology's Revolutionary Benefits

Antioxidants	DII® Technology
Retroactive: Antioxidants attempt to battle free radicals by neutralizing them	**Proactive:** **DII® removes iron, a core component in the process that creates free radicals, from the surface of the skin**

By clearing iron from the surface of the skin before it can react to sunlight, FE:I Beauty Tech's D.I.I. technology exfoliates the basis of free radicals on the surface of the skin. Doing something no other cosmetic product can do. Antioxidants, including Retinol, Vitamin E, Resveratrol and Niacinamide, can only address free radicals after the free radicals are activated.

DII® CLINICAL TRIAL

Researchers put this groundbreaking discovery in anti-aging to the test in clinical studies of an eye cream and face cream incorporating FE:I Beauty Tech's proprietary D.I.I. technology. The separate trials sought to evaluate the efficacy of the two anti-aging products over a 42-day period in a range of anti-aging categories.

The two open label trials included women with mild to moderate fine lines and wrinkles in the area under study as determined by a trained technician. Thirty (30) participants were enrolled in the eye cream study and 31 were enrolled in the study of the face cream. The women in both studies agreed to abstain from using any anti-aging, sun-protection and moisturizing products during the 7-day washout period and for the entire duration of the studies. During the 7-day washout period, the women participating in the studies used only Ivory® Soap issued by the lab and continued to only use the assigned soap and assigned test product for the entire remaining test periods.

The anti-aging benefits of FE:I Beauty Tech's D.I.I. technology were assessed at set evaluation points (immediate, day 3, 7, 14, 28 and 42) using Visual Expert Grading as an objective method and subjectively using panelist self-assessment questionnaire responses.

Researchers also performed bioinstrumental measurements on a subset of study participants for skin hydration, elasticity and viscoelasticity in the eye or face (depending on the study) and the inner forearm. These measurements helped researchers compare how D.I.I. technology affects skin damage caused by ultraviolet light versus the inevitable (intrinsic) aging process. The inner forearm, generally protected from sunlight, was used to represent intrinsic skin aging, which occurs naturally and is affected by the degenerative effects of free radicals, hormonal shifts and the body's inability to perfectly repair skin damage. This type of damage results in thin, dry skin, fine wrinkles and gradual dermal atrophy aged skin. In contrast, skin on the facial area represented extrinsically aged skin, which is caused by external factors, such as UV radiation, cigarette smoking, air pollution and poor nutrition, resulting in coarse wrinkles, loss of elasticity, laxity and rough texture appearance.

> ***91%*** *of women on day 7 and* ***100%*** *at final evaluation (day 42) reported*
>
> ✓ ***Softer and more hydrated*** *looking skin*
>
> ✓ ***Smoother*** *looking skin*
>
> ✓ ***Healthier*** *looking and feeling skin*

Objective/Bioinstrumental Test Methods

The Visual Grading Scale

Three trained clinical evaluators graded each study participant on an 11-point intensity grading scale for fine lines, wrinkles, brightness and firmness, and found statistically significant improvements in all evaluated skin parameters when compared to the baseline at every evaluation point.

Skin Hydration

Novameter readings, which use electroconductivity to measure how much water is in the skin, demonstrated statistically significant increases in mean moisturization.

Firmness and Elasticity

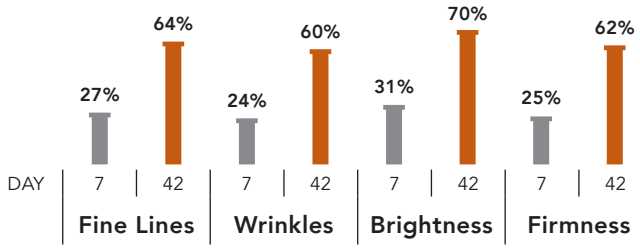
Cutometer readings, in which suction is applied to the skin in order to measure the skin's resistance to suction (firmness) and its ability to return into its original state (elasticity), demonstrated statistically significant improvement in both measures at each evaluation time point.

Clinical Trial Results: Eye Cream Incorporating DII® Technology

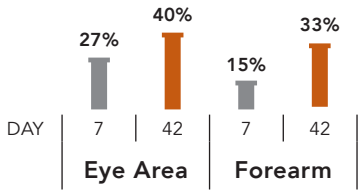
In their questionnaire responses, most participants agreed that skin around the eyes looked and felt protected, smoother, healthier, stronger, brighter, firmer and more hydrated at each evaluation time point, and that they would recommend this product to family and friends. Moreover, most agreed that fine lines and wrinkles around the eyes were noticeably diminished and that the look of dark circles and puffiness under the eyes had been reduced after using the test product for seven days and at all consecutive time points. In addition, the majority agreed that the test product is gentle enough for everyday use.

In the biomechanical tests conducted on the eye and forearm areas representing areas with high and low UV exposure, respectively, participants saw more improvement in the eye area due to the synergistically harmful interaction between iron and ultraviolet light. Visual Expert Grading performed by trained clinical evaluators and biophysical measurements supported what the women saw in the mirror.

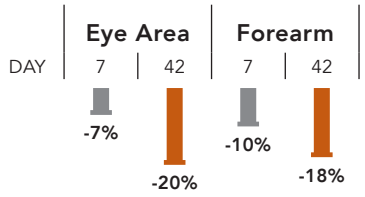
Trained Clinical Evaluator Scores
(% improvement)



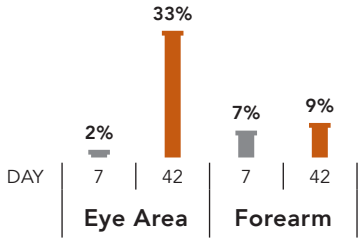
Hydration Readings
(% improvement)



Skin Final Distension
(A decrease in stretch demonstrates improved firmness, thickness, and tightness.)



Overall Elasticity
(% improvement)



Case Study

A legally blind participant could not see the results but testified to the improved texture and stated that her skin felt more youthful. She has since turned down other trials in order to continue the D.I.I. regimen.

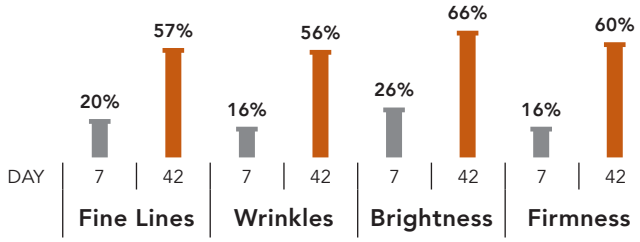
Baseline | 15 Minutes | Day 3 | Day 14 | Day 28 | Day 42

Clinical Trial Results: Face Cream Incorporating DII® Technology

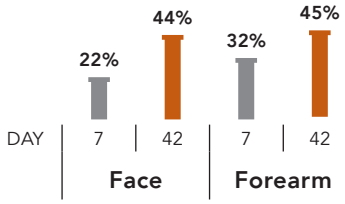
A majority of participants agreed at every evaluation point that their faces looked and felt protected, firmer, smoother, healthier, stronger, brighter, more hydrated, more even-toned and elastic with more bounce, and that skin appeared clearer with fewer skin blemishes. Most also agreed that pores looked smaller after using the test product for three consecutive days and at each consecutive time point. Moreover, the majority agreed that fine lines and wrinkles in the face area have been noticeably diminished after seven days of use and at each consecutive time point. The majority would recommend this product to family and friends.

In the biomechanical tests conducted on the face and forearm areas representing areas with high and low UV exposure, respectively, participants saw more improvement in the face area due to the synergistically harmful interaction between iron and ultraviolet light. Subjective questionnaire responses corroborated the information obtained from Visual Expert Grading performed by trained clinical evaluators and biophysical measurements.

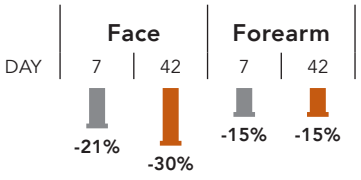
Trained Clinical Evaluator Scores
(% improvement)



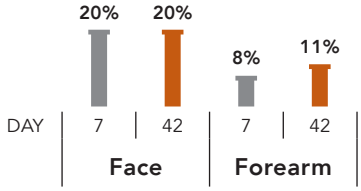
Hydration Readings
(% improvement)



Skin Final Distension
(A decrease in stretch demonstrates improved firmness, thickness, and tightness.)



Overall Elasticity
(% improvement)



Case Study

A 55 year-old woman who has smoked cigarettes since the age of 19 had visual wrinkle improvement within 15 minutes and a reduction of wrinkles at every time point measured. The participant's results are consistent with the higher levels of stored iron typically seen in smokers, even after quitting.

Baseline | 15 Minutes | Day 3 | Day 14 | Day 28 | Day 42

KEY TAKEAWAYS

- While iron is essential for normal physiological functions, **excess iron promotes the production of damage-inducing hydroxyl free radicals which leads to visible signs of aging**.
- The body uses skin to rid itself of iron, which is stored on the surface of the skin and—after a chemical process induced by sunlight--can produce hydroxyl free radicals, leading to skin damage. Iron and sunlight also work together to enhance the activity of collagenase-1, an enzyme that breaks down collagen and elastin, contributing to the appearance of fine lines and wrinkles.
- **Increased iron as a result of menopause**—after which women can no longer lose iron through menstruation—**is potentially a key determinant to visible signs of skin aging after menopause**.
- **FE:I Beauty Tech has developed a safe method to exfoliate iron from the surface of the skin to reduce the appearance of fine lines and wrinkles in a new way by reducing the opportunity for free radicals to form on the surface of the skin.** In a clinical trial of its eye cream and face cream, women saw improvement across every measure in objective, subjective and biomechanical tests.

ABOUT XI HUANG, PH.D.

Xi Huang has investigated iron's role in diseases for more than three decades and is credited in more than 80 peer-reviewed publications, many of which demonstrate that excess iron is an important risk factor in women's health. Dr. Huang's research laboratory has shown that iron accumulation due to the cessation of menstruation in older postmenopausal women contributes to osteoporosis and skin aging. Dr. Huang began his research into the negative effects of too much iron as a Ph.D. student at the Université Paris VII, where he identified that bioavailable iron in mixed coal dusts is the active compound in inducing oxygen free radicals. Subsequently, he confirmed the role of iron in the Appalachian coals (e.g., West Virginia, Pennsylvania, Kentucky) in coal dust-induced pneumoconiosis, also known as black lung disease. In the course of this research, Dr. Huang discovered that the addition of calcite to Appalachian coals could prevent iron from becoming bioavailable, leading him to develop De-Ironizing Inducer (D.I.I.) technology, which can neutralize iron in skin to reduce the opportunity for the formation of free radicals by reducing the accumulation of iron on the surface of the skin. Dr. Huang is the founder and president of FE:I Beauty Tech. He also serves as the chief technology officer of Ex Vivo Dynamics, Inc., where he guides the development of a medical device that will improve blood transfusions. He also teaches r at NYU School of Medicine. Dr. Huang received his Ph.D. and M.S. in toxicology and applied pharmacology from the Université Paris VII and received his undergraduate degree from China Agricultural University.

ENDNOTES

i Barbusinski K. Henry John Horstman Fenton-short biography and brief history of Fenton reagent discovery, Metrologia, 2009 Jan; 14: 101-105. https://www.researchgate.net/publication/285872170_Henry_John_Horstman_Fenton_-_short_biography_and_brief_history_of_Fenton_Reagent_Discovery

ii Weintraub L R, Demis D J, Conrad M E, Crosby W H. Iron excretion by the skin Selective localization of iron-59 in epithelial cells. Am J Pathol. 1965 Jan; 46(1): 121–127. https://pubmed.ncbi.nlm.nih.gov/14253125/

iii Sullivan J L. Iron and The Sex Difference in Heart Disease Risk. Lancet. 1981 Jun 13;1(8233):1293-4. https://pubmed.ncbi.nlm.nih.gov/6112609/

iv Halliwell B, Gutteridge J M C. Oxygen toxicity, oxygen radicals, transition metals and disease. The Biochemical Journal. 1984;219(1):1–14. https://pubmed.ncbi.nlm.nih.gov/6326753/

v Stevens R G, Beasley R P, Blumberg B S. Iron-binding proteins and risk of cancer in Taiwan. J Natl Cancer Inst. 1986 Apr;76(4):605-10. https://pubmed.ncbi.nlm.nih.gov/3007843/

vi Huang X, Zalma R, Pezerat H. Factors that influence the formation and stability of hydrated ferrous sulfate in coal dusts. Possible relation to the emphysema of coal miners. Chem Res Toxicol. May-Jun 1994;7(3):451-7. https://pubmed.ncbi.nlm.nih.gov/8075379/

vii Pourzand C, Watkin R D, Brown J E, Tyrrell R M. Ultraviolet A radiation induces immediate release of iron in human primary skin fibroblasts: The role of ferritin. Proc Natl Acad Sci USA. 1999 Jun 8;96(12):6751-6. https://pubmed.ncbi.nlm.nih.gov/10359784/

viii Pelle E, Jian J, Zhang Q, Muizzuddin N, Yang Q, Dai J, Maes D, Pernodet N, Yarosh D B, Frenkel K, Huang X. Menopause increases the iron storage protein ferritin in skin. J Cosmet Sci. May-Jun 2013;64(3):175-9. https://pubmed.ncbi.nlm.nih.gov/23752032/

ix Yang Q, Jian J, Katz S, Abramson S B, Huang X. 17β-Estradiol inhibits iron hormone hepcidin through an estrogen responsive element half-site. Endocrinology. 2012 Jul;153(7):3170-8. https://pubmed.ncbi.nlm.nih.gov/22535765/