Fagron genomics

TrichoTest™ Literature review

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Introduction

The TrichoTest™ literature review contains the most relevant scientific articles that support the genetic analysis performed in TrichoTest™. Some suggested APIs and DCIs are not directly associated with a genetic variation but have an important role in the metabolic pathways analyzed. For more detailed information regarding the analyzed genes and their relationship with APIs/DCIs for alopecia treatment, please be referred to TrichoTest™ Scientific validation document.

Should you have any questions or remarks, please contact your local sales representative.

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Literature review – Genetic factors

1. Prostaglandin metabolic pathways

1.1 GPR44 mutation leads to increased Prostaglandin D2 receptor expression and inflammation.

Indication: Androgenetic alopecia.
Related APIs: Prostaquinon™, Cetirizine.

Campos Alberto E, et al. *The single nucleotide polymorphism CRTh2 rs533116 is associated with allergic asthma and increased expression of CRTh2*. Allergy. 2012 Nov;67(11):1357-64. doi: 10.1111/all.12003.

Objective: to assess the association between the CRTh2 (GPR44) mutation rs533116, expression levels of GPR44 and inflammation.
Methods: CRTh2 rs533116 was genotyped in an ethnically diverse population (n=1282). The proportion of cells expressing CRTh2 was determined in peripheral blood from subjects with allergic airways disease and controls, as well as with in vitro differentiated Th2 cells. Receptor function was assessed by stimulating Th2 cells with the CRTh2-specific agonist 13,14-dihydro-15-keto-PGD2 (DKPGD2) and measuring IL-4 and IL-13 by intracellular staining and ELISA.
Conclusions: the AA genotype was significantly associated with higher expression of CRTh2 ($P<0.05$).

1.2 GPR44 mutation leads to an increased mRNA half-life of the Prostaglandin D2 receptor.

Indication: Androgenetic alopecia.
Related APIs: Prostaquinon™, Cetirizine.

Huang JL, et al. *Sequence variants of the gene encoding chemoattractant receptor expressed on Th2 cells (CRTH2) are associated with asthma and differentially influence mRNA stability*. Hum Mol Gen. 2004 Nov; 13(21): 2691–2697. doi:10.1093/hmg/ddh279

Objective: assess the association between the CRTh2 (GPR44) mutation rs545659, allergic inflammation risk and higher levels of mRNA stability.
Methods: CRTh2 rs533116 was genotyped in an ethnically diverse population (n=248). Stability studies of the mRNA was studied by Tet-regulated reporter constructs experiments (pTet-CRTH2GG vs pTet-CRTH2AC).
Conclusions: the GG genotype of the GPR44 receptor showed an increased mRNA stability (half-life of mRNA) ($P<0.01$).

1.3 PTGFR mutations increase the likelihood of a positive response to Latanoprost.

Indication: Androgenetic alopecia.
Related APIs: Latanoprost.

Ussa F, et al. *Association between SNPs of Metalloproteinases and Prostaglandin F2α Receptor Genes and Latanoprost Response in Open-Angle Glaucoma*. Ophthalmology. 2015 May;122(5):1040-8.e4. doi: 10.1016/j.ophtha.2014.12.038.

Objective: assess the association between Prostaglandin F2α receptor gene (PTGFR) mutations and response to Latanoprost.

Methods: a multi-SNP haplotype analysis was performed on 117 patients. Treatment efficacy was addressed after a minimum of 4 weeks of treatment with Latanoprost, following the LSG criteria in terms of IOP reduction to define responders and non-responders to Latanoprost.
Conclusions: genotypic association showed that rs10782665 (OR, 0.22), rs6686438 (OR, 0.2) and rs1328441 (OR, 0.33) increased the likelihood of a positive response to Latanoprost.

1.4 Mutations in the PTGES2 lead to reduced levels of PGE2 and a need to increase them for the alopecia treatments.

Indication: Androgenetic alopecia.
Related APIs: Minoxidil.

Fischer A, et al. *Association Analysis Between the Prostaglandin E Synthase 2 R298H Polymorphism and Body Mass Index in 8079 Participants of the KORA Study Cohort*. Genet Test Mol Biomarkers. 2009 Apr;13(2):223-6. doi: 10.1089/gtmb.2008.0111.

Objective: explore the association between the PTGES2 R298H SNP and body mass index (BMI).
Methods: the R298H SNP (rs13283456) and three haplotypes (rs884115, rs10987883, and rs4837240) were analyzed, covering a 20 kb gene region in population-based surveys of the Kooperative Gesundheitsforschung in der Region Augsburg study cohort with 8079 participants.
Conclusions: the heterozygous genotype leads to a slight reduction in overall PTGES2 function, causing a reduced PGE2 level. This could result in a lower BMI, due to PGE2's antilipolytic and adipocyte hypertrophy activities. An even stronger reduction of PGE2 levels in homozygous carriers of the PTGES2 298H allele may induce compensatory upregulation of other PTGES2 enzymes.

1.5 SULT1A1*2 genotype is associated with low enzyme activity and thermal stability.

Indication: Androgenetic alopecia.
Related APIs: Minoxidil.

Raftogianis RB, et al. *Phenol sulfotransferase pharmacogenetics in humans: Association of common SULT1A1 alleles with TS PST phenotype*. Biochem Biophys Res Commun. 1997;239:298–304. http://dx.doi.org/10.1006/bbrc.1997.7466.

Objective: assessment of the association between polymorphisms in SULT1A and enzymatic activity modulations.
Methods: the biochemical assay associated with the enzyme encoded by SULT1A1 is the thermal stable (TS) sulfation of 4 microM 4-nitrophenol (TS PST activity). 33 subjects were genotyped for SULT1A1*2 and TS studies were performed.
Conclusions: SULT1A1*2 genotype was associated with decreased activity and low thermal stability.

2. Androgenetic metabolic pathways

2.1 Mutations on the SDR5A gene lead to increased enzymatic activity and hyperandrogenism.

Indication: Androgenetic alopecia.
Related APIs: Finasteride/Dutasteride.

Goodarzi MO, et al. *Variants in the 5α-Reductase Type 1 and Type 2 Genes Are Associated with Polycystic Ovary Syndrome and the Severity of Hirsutism in Affected Women*. J Clin Endocrinol Metab. 2006 Oct; 91(10):4085-91.

Objective: address the association between SDR5A variants and the hyperandrogenism.
Methods: 475 patients were genotyped for SD1R5A1 and SRD5A2 mutations.
Conclusions: the SDR5A1 and SDR5A2 mutations were associated with increased hyperandrogenism and hirsutism (P<0.05). Hyperandrogenism was linked to a potential increase of the 5α-reductase activity, as it is often observed in obesity.

2.2 SRD5A2 enzymatic reaction is inhibited by Finasteride.

Indication: Androgenetic alopecia.
Related APIs: Finasteride.

Libecco JF, et al. *Finasteride in the treatment of alopecia*. Expert Opin Pharmacother. 2004 Apr;5(4):933-40.

Objective: review of the state-of-the-art information regarding Finasteride use on alopecia treatment.
Methods: metanalysis of scientific publications
Conclusions: Finasteride is a 5α-reductase inhibitor approved for the treatment of hair loss in AGA, inhibiting the conversion of testosterone to dihydrotestosterone (DHT) a potent Androgenetic molecule.

2.3 SRD5A1 and SRD5A2 are inhibited by Dutasteride.

Indication: Androgenetic alopecia.
Related APIs: Dutasteride.

Arif T, et al. *Dutasteride in Androgenetic Alopecia*. An Update. Curr Clin Pharmacol. Curr Clin Pharmacol. 2017;12(1):31-35. doi: 10.2174/1574884712666170310111125.

Objective: review of the current status of Dutasteride in androgenetic alopecia.
Methods: metanalysis of scientific publications.
Conclusions: Dutasteride is a key inhibitor of the 5α-reductase isoforms 1 and 2.

2.4 CYP19 mutations lead to an increased aromatase activity and an imbalance in the estradiol/testosterone (E2/T) ratio.

Indication: Androgenetic alopecia.
Related APIs: Estradiol.

Zhang XL, et al. *SNP rs2470152 in CYP19 is correlated to aromatase activity in Chinese polycystic ovary syndrome patients.* Mol Med Rep. 2012 Jan;5(1):245-9. doi: 10.3892/mmr.2011.616.

Objective: to associate CYP19 mutations with aromatase activity levels.
Methods: 661 individuals were genotyped and hormone levels were analyzed among various genotypes. Statistical analyses were performed in order to link genotype and hormonal imbalance.
Conclusions: the TC genotype of the rs2470152 CYP19 mutation may inhibit aromatase activity and thus result in hyperandrogenism.

2.5 CYP19 mutations are clearly associated with serum E2 (estradiol) and E1 (estrone) levels.

Indication: Androgenetic alopecia.
Related APIs: Estradiol.

Eriksson AL, et al. *Genetic Variations in Sex Steroid-Related Genes as Predictors of Serum Estrogen Levels in Men*. J Clin Endocrinol Metab. 2009 Mar; 94(3): 1033–1041. doi:10.1210/jc.2008-1283.

Objective: identify genetic variations associated with serum levels of sex steroids.
Methods: 604 SNPs were genotyped in 50 genes of three different populations (n=1041; n=2568; n=1922). Serum E2, testosterone and estrone (E1) levels were analyzed using gas chromatography/mass spectrometry.
Conclusions: SNP rs2470152 of the CYP19 gene is associated with serum E2 and E1 levels in men. ($p<0.001$).

2.6 Ginseng is associated with inhibition of DHT-induced androgen receptor transcription.

Indication: Androgenetic alopecia.
Related APIs: Ginseng.

Park GH, et al. *Red Ginseng Extract Promotes the Hair Growth in Cultured Human Hair Follicles*. J Med Food. 2015 Mar 1; 18(3): 354–362.

Objective: to investigate the hair growth-promoting effects of red ginseng extract (RGE) and its ginsenosides.
Methods: the proliferative activities of cultured human hair follicles treated with RGE and ginsenoside-Rb1 were assessed using Ki-67 immunostaining. Their effects on isolated human dermal papilla cells (hDPCs) were evaluated using cytotoxicity assays, immunoblot analysis of signaling proteins and determination of growth factors.
Conclusions: RGE and its ginsenosides may enhance hDPC proliferation, activate ERK and AKT signaling pathways in hDPCs, upregulate hair matrix keratinocyte proliferation, and inhibit the DHT-induced androgen receptor transcription. These results suggest that red ginseng may promote hair growth in humans.

3. Anti-inflammatory metabolic pathways

3.1 Mutations on the Glucocorticoid receptors (GR) are promising pharmacogenomics markers of GC response.

Indication: Alopecia Areata.
Related APIs: Clobetasol, Triamcinolone, Hydrocortisone.

Gasic V, et al. *Pharmacogenomic markers of glucocorticoid response in the initial phase of remission induction therapy in childhood acute lymphoblastic leukemia*. Radiol Oncol. 2018 Sep 11;52(3):296-306. doi: 10.2478/raon-2018-0034.

Objective: to analyze variants in several pharmacogenes (NR3C1, GSTs and ABCB1) with potential contribution to improvement of glucocorticoids (GC) response through personalization of GC therapy.
Methods: retrospective study of 122 patients analyzing GR receptor mutations. The marker of GC response was blast count per microliter of peripheral blood on treatment day 8. An analysis was carried out in which cut-off value for GC response was 1000 (according to Berlin-Frankfurt-Munster [BFM] protocol), as well as 100 or 0 blasts per microliter.

Conclusions: the rs6198 variant is located in the 3' UTR region exon 9β, in the "ATTTA" motif of an isoform of GR with drastically lower affinity for glucocorticoids. If the minor rs6198 G allele is present, the mRNA becomes more stable and it leads up to greater translation of the isoform of GR with lower affinity for glucocorticoids.

4. Vitamins metabolic pathways

4.1 A genetic variation of the CRABP2 gene leads to 4.4 fold increase of retinoic acid levels in serum.

Indication: Androgenetic alopecia.
Related APIs: Retinoic Acid (vit. A).

Manolescu DC, et al. *Newborn serum retinoic acid level is associated with variants of genes in the retinol metabolism pathway*. Pediatr Res. 2010 Jun;67(6):598-602. doi: 10.1203/PDR.0b013e3181dcf18a.

Objective: to identify genetic variations in the retinol metabolism pathway that are associated to serum retinoic Acid (RA) levels.
Methods: RA levels and DNA mutations were measured in n= 145 health Caucasian infants from Montreal.
Conclusions: homozygosity for the (A) allele of the SNP in the CRABP2 gene was associated with 4.4-fold increase in umbilical cord serum RA. CRABP2 facilitates RA binding to its cognate receptor complex and transfer to the nucleus.

4.2 A genetic variation of the BTD gene leads to a 48% normal serum activity of the biotinidase enzyme.

Indication: Androgenetic alopecia.
Related APIs: Retinoic Acid (vit. A).

Swango KL, et al. *Partial biotinidase deficiency is usually due to the D444H mutation in the biotinidase gene. Partial biotinidase deficiency is usually due to the D444H mutation in the biotinidase gene*. Hum Genet. 1998 May;102(5):571-5.

Objective: identification of genetic variations associated with biotinidase deficiency.
Methods: 19 individuals with partial biotinidase deficiency were identified by newborn screening conducted in the United States and in several foreign countries. Blood was obtained from these children and from their parents and siblings when possible.
Conclusions: D444H mutation results in a 48% of mean normal serum activity.

5. Vasodilatation and blood circulation pathways

5.1 ACE increased levels are found in patients with alopecia areata.

Indication: Alopecia areata.
Related APIs: Carnitine, Coenzyme-Q10, Arginine, Caffeine, Gingko biloba.

Namazi MR, et al. *Angiotensin converting enzyme activity in alopecia areata*. Enzyme Res. 2014; 2014:694148. doi: 10.1155/2014/694148.

Objective: to address the correlation between alopecia areata (AA) and increased levels of angiotensin converting enzyme (ACE).
Methods: ACE activity was measured in 19 patients with AA and 16 healthy control subjects.
Conclusions: serum ACE activity was higher in the patient group (55.81 U/L) compared to the control group (46.41 U/L) (P=0.085).

5.2 Genotype GG on ACE variations leads to increased ACE activity and blood pressure.

Indication: Androgenetic alopecia/Alopecia areata.
Related APIs: Minoxidil, Carnitine, Coenzyme-Q10, Arginine, Caffeine, Gingko biloba.

Firouzabadi N, et al. *Association of angiotensin-converting enzyme (ACE) gene polymorphism with elevated serum ACE activity and major depression in an Iranian population*. Psychiatry Res. 2012 Dec 30;200(2-3):336-42. doi: 10.1016/j.psychres.2012.05.002.

Objective: to associate ACE variations with elevated serum ACE activity.
Methods: 295 patients were genotyped and measured for angiotensin activity.
Conclusions: GG genotype of gene ACE variation A2350G was significantly associated with higher serum ACE activity ($p<0.001$) and higher diastolic pressure ($p<0.05$).

5.3 L-arginine can induce nitric oxide-dependent vasodilation.

Indication: when vasodilation pathway is affected in the patient is intolerant to caffeine.
Related APIs: Arginine.

Bode-Böger SM, et al. *L-arginine induces nitric oxide-dependent vasodilation in patients with critical limb ischemia. A randomized, controlled study*. Circulation. 1996 Jan 1;93(1):85-90.

Objective: evaluation of vasodilation potential of arginine.
Methods: evaluation of the effects of one intravenous infusion of L-arginine (30 g, 60 minutes) or PGE1 (40 microgram, 60 minutes) versus placebo (150 mL 0.9% saline, 60 minutes) on blood pressure, peripheral hemodynamics and urinary NO3- and cGMP excretion rates in patients with critical limb ischemia.
Conclusions: intravenous L-arginine induces NO-dependent peripheral vasodilation in patients with critical limb ischemia. Increased urinary NO3- excretion may be a sum effect of NO synthase substrate provision (L-arginine) and increased shear stress (PGE1 and L-arginine).

6. Collagen metabolic pathways

6.1 COL1A1 overexpression is associated to Androgenetic Alopecia in young men.

Indication: Androgenetic alopecia.
Related APIs: Minoxidil, Silicium Max, MSM, Adenosin.

Michel L, et al. *Study of gene expression alteration in male androgenetic alopecia: evidence of predominant molecular signaling pathways*. Br J Dermatol. 2017 Nov;177(5):1322-1336. doi: 10.1111/bjd.15577.

Objective: determine the gene expression alterations in male Androgenetic alopecia.

Methods: 28 male young caucasian volunteers were selected for the study and allocated into the two following groups - 14 hairless/bald participants (age: 29.4±3.4), with premature AGA, with stage V to VII according to the Hamilton's classification as modified by Norwood, and 14 control subjects (age: 26.1±3.6) with <2% white hairs and stage I or II in the Hamilton's classification as modified by Norwood.
Conclusions: COL1A1 was statistically overexpressed in AGA male patients.

6.2 COL1A1 mutation leads to an increased expression of COL1A1 creating imbalance between α1 and α2 protein chains.

Indication: Androgenetic alopecia.
Related APIs: Minoxidil, Silicium Max, MSM, Adenosin.

Stępien-Słodkowska M, et al. *The +1245g/t polymorphisms in the collagen type I alpha 1 (COL1A1) gene in polish skiers with anterior cruciate ligament injury*. Biol Sport. 2013 Mar;30(1):57-60. doi: 10.5604/20831862.1029823.

Objective: to examine the association of +1245G/T polymorphisms in the COL1A1 gene with anterior cruciate ligament (ACL) ruptures in Polish male recreational skiers in a case-control study.
Methods: a total of 138 male recreational skiers with surgically diagnosed primary ACL ruptures, all of whom qualified for ligament reconstruction, were recruited for the study. The control group comprised 183 apparently healthy male skiers with a comparable level of exposure to ACL injury, none of whom had any self-reported history of ligament or tendon injury. DNA samples extracted from the oral epithelial cells were genotyped for the +1245G/T polymorphisms using real-time PCR method.
Conclusions: the G to T substitution in an intronic Sp1 binding site (rs1800012) resulted in increased affinity for the transcription factor Sp1 and increased collagen a1 expression vs collagen a2.

7. Insulin metabolic pathways

7.1 IGF-I has a significant effect on the rate of linear hair growth and extended the overall anagen phase

Indication: Androgenetic alopecia.
Related APIs: IGrantine-F1™.

Ahn SY, et al. *Effect of IGF-I on Hair Growth Is Related to the Anti-Apoptotic Effect of IGF-I and Up-Regulation of PDGF-A and PDGF-B*. Ann Dermatol. 2012 Feb;24(1):26-31. doi: 10.5021/ad.2012.24.1.26.

Objective: to observe potential relationships between IGF-I and other factors (i.e. apoptosis related molecules, pro-inflammatory cytokines, other growth factors, etc.) in the control of hair follicle (HF) growth.
Methods: the effect of IGF-I on human hair growth was measured using an organ culture model of human HFs and compared with a control group that did not receive IGF-I.
Conclusions: the effect of IGF-I on hair growth appears to be related to the upregulation of PDGF-A and PDGF-B and to the anti-apoptotic effect of IGF-I.

7.2 IGFR-1 mutations correlate to lower serum IGF-1 levels

Indication: Androgenetic alopecia.
Related APIs: IGrantine-F1™.

Gately K, et al. *Mutational analysis of the insulin-like growth factor 1 receptor tyrosine kinase domain in non-small cell lung cancer patients*. Mol Clin Oncol. 2015 Sep; 3(5): 1073–1079. doi: 10.3892/mco.2015.580.

Objective: to associate IGFR-1 mutations with pathological conditions.
Methods: 866 control patients and 198 patients were genotyped for several IGFR-1 mutations.
Conclusions: subjects carrying at least an A allele at the rs2229765 SNP of IGFR-1 have low free plasma IGF1 levels.

Literature review – Non-genetic factors

8. Prostaglandin metabolic pathways

8.1 Topical cetirizine is related to an improvement on the initial framework of andogenetic alopecia.

Indication: patients with proper enzymatic response to PGD2 and possible allergy to Prostaquinon™.
Related APIs: cetirizine.

Rossi A, et al. *A preliminary study on topical cetirizine in the therapeutic management of androgenetic alopecia*. J Dermatolog Treat. 2018 Mar;29(2):149-151.

Objective: to evaluate the efficacy of topical cetirizine versus placebo in patients with AGA.
Methods: a sample of 85 patients was recruited, of which 67 were used to assess the effectiveness of the treatment with topical cetirizine, while 18 were control patients.
Conclusion: it was found that the main effect of cetirizine was an increase in total hair density, terminal hair density and diameter variation from T0 to T1, while the vellus hair density shows an evident decrease. The results have shown that topical cetirizine 1% is responsible for a significant improvement of the initial framework of AGA.

9. Androgenetic metabolic pathways

9.1 Ginseng is associated with inhibition of DHT-induced androgen receptor transcription.

Indication: patients that requires anti-androgenic treatments and the expected efficacy of estradiol, finasteride and dutasteride is low.
Related APIs: ginseng.

Park GH, et al. *Red Ginseng Extract Promotes the Hair Growth in Cultured Human Hair Follicles*. J Med Food. 2015 Mar 1; 18(3): 354–362.

Objective: to investigate the hair growth-promoting effects of red ginseng extract (RGE) and its ginsenosides.
Methods: the proliferative activities of cultured human hair follicles treated with RGE and ginsenoside-Rb1 were assessed using Ki-67 immunostaining. Their effects on isolated human dermal papilla cells (hDPCs) were evaluated using cytotoxicity assays, immunoblot analysis of signaling proteins and determination of growth factors.
Conclusions: RGE and its ginsenosides may enhance hDPC proliferation, activate ERK and AKT signaling pathways in hDPCs, upregulate hair matrix keratinocyte proliferation, and inhibit the DHT-induced androgen receptor transcription. These results suggest that red ginseng may promote hair growth in humans.

9.2 Topical melatonin solution has a positive effect in the treatment of androgenic alopecia.

Indication: patients that requires anti-androgenic treatments and the expected efficacy of estradiol, finasteride and dutasteride is low.
Related APIs: melatonin.

Fischer TW, et al. *Topical Melatonin for Treatment of Androgenetic Alopecia*. Int J Trichology. 2012 Oct-Dec; 4(4): 236–245.

Objective: to evaluate the potential of topical Melatonin for androgenetic alopecia treatment.
Methods: one pharmacodynamic study on topical application of melatonin and four clinical pre-post studies were performed in patients with androgenetic alopecia or general hair loss and evaluated by standardized questionnaires, TrichoScan, 60-second hair count test and hair pull test.
Conclusions: five clinical studies showed positive effects of a topical melatonin solution in the treatment of AGA in men and women while showing good tolerability. Since safety and tolerability in all of the studies was good, the topical application of a cosmetic melatonin solution can be considered as a treatment option in androgenetic alopecia.

9.3 Serenoa serrulata is associated with decreased uptake of DHT by hair follicles.

Indication: patients that have a good response to finasteride but are not able to use it due to intolerance or side effects.
Related APIs: Serenoa serrulata.

Reddy V, et al. *Saw palmetto extract: A dermatologist's perspective*. Indian J Drugs Dermatol 2017;3:11-3.

Saw Palmetto, known also as Serenoa repens (SR) or Serenoa serrulate, is a small palm tree native to eastern regions of the United States. Its extract is believed to be a highly effective antiandrogen as it contains phytoesterols and fatty acids as its major ingredient.
SR has proved to be effective in the management of AGA. Apart from the primary mechanism of action of 5 alpha-reductase blockade, SR is thought to decrease the uptake of DHT by the hair follicles and decrease its binding to androgenic receptors. Another possible effect of SR in AGA seen with its liposterolic extract is suppression of lipopolysaccharide-activated gene expression of chemokines, including CCL 17, CXCL 6, and LT B 4 associated inflammatory and apoptotic pathways. Hence, its anti-inflammatory properties are of value in AGA. With SR growth of hair is prevalently seen over the frontal and temporal regions of the scalp.

10. Vitamins and minerals metabolic pathways

10.1 Female pattern hair loss patients present lower levels of iron.

Indication: anemia; patients with heavy menstruation flux.
Related APIs: iron sulfate.

Park SY, et al. *Iron Plays a Certain Role in Patterned Hair Loss*. J Korean Med Sci. 2013 Jun; 28(6): 934–938.

Objective: to evaluate the relationship between iron and hair loss.
Methods: retrospective chart review was conducted on patients with female pattern hair loss (FPHL) and male pattern hair loss (MPHL). All patients underwent screening including serum ferritin, iron, and total iron binding

capacity (TIBC), CBC, ESR and thyroid function test. For normal healthy controls, age-sex matched subjects who had visited the hospital for a check-up with no serious disease were selected. A total 210 patients with FPHL (n = 113) and MPHL (n = 97) with 210 healthy controls were analyzed.
Conclusions: serum ferritin concentration (FC) was lower in patients with FPHL (49.27 ± 55.8 µg/L), compared with normal healthy women (77.89 ± 48.32 µg/L) (P < 0.001). Premenopausal FPHL patients turned out to show much lower serum ferritin than age/sex-matched controls (P < 0.001). Among MPHL patients, 22.7% of them showed serum FC lower than 70 µg/L, while no one had serum FC lower 70 µg/L in healthy age matched males. These results suggest that iron may play a certain role especially in premenopausal FPHL.

11. Vasodilatation and blood circulation pathways

11.1 L-arginine can induce nitric oxide-dependent vasodilation.

Indication: patients with affected vasodilation pathway and intolerance to caffeine.
Related APIs: arginine.

Bode-Böger SM, et al*. L-arginine induces nitric oxide-dependent vasodilation in patients with critical limb ischemia. A randomized, controlled study*. Circulation. 1996 Jan 1;93(1):85-90.

Objective: evaluation of vasodilation potential of arginine.
Methods: evaluation of the effects of one intravenous infusion of L-arginine (30 g, 60 minutes) or PGE1 (40 microgram, 60 minutes) versus placebo (150 mL 0.9% saline, 60 minutes) on blood pressure, peripheral hemodynamics and urinary NO3- and cGMP excretion rates in patients with critical limb ischemia.
Conclusions: intravenous L-arginine induces NO-dependent peripheral vasodilation in patients with critical limb ischemia. Increased urinary NO3- excretion may be a sum effect of NO synthase substrate provision (L-arginine) and increased shear stress (PGE1 and L-arginine).

11.2 L-arginine is associated with a protective effect on hair damage via oxidative colouring process.

Indication: when patients use hair dyes.
Related APIs: arginine.

Oshimura E, et al. *Effects of arginine on hair damage via oxidative coloring process*. J Cosmet Sci. 2004; 55 Suppl: S155-70.

Objective: to measure the protective effects of arginine in oxidative coloring or bleaching process.
Methods: contact angle measurement, tensile measurement and amino acid analysis were employed.
Conclusion: results suggest that arginine prevents the undesirable attack by hydrogen peroxide on hair proteins and hair surface lipids. Furthermore, it is also suggested from amino acid analysis that a considerable amount of arginine is deposited on, or in hair fibers from coloring agents.

11.3 L-Carnitine ameliorates the oxidative stress response to angiotensin II.

Indication: patients with affected vasodilation pathway and intolerance to caffeine.
Related APIs: L-carnitine.

Blanca AJ, et al. *L-Carnitine ameliorates the oxidative stress response to angiotensin II by modulating NADPH oxidase through a reduction in protein kinase c activity and NF-κB translocation to the nucleus*. Food Chem. 2017 Aug 1;228:356-366.

Objective: to investigate the signalling pathways involved in the effect of L-carnitine (LC) on angiotensin II (Ang II)-induced NADPH oxidase activation in NRK-52E cells.
Conclusion: Ang II increased the generation of superoxide anion from NADPH oxidase, as well as the amount of hydrogen peroxide and nitrotyrosine. Co-incubation with LC managed to prevent these alterations and also reverted the changes in NADPH oxidase expression triggered by Ang II. Cell signalling studies evidenced that LC did not modify Ang II-induced phosphorylation of Akt, p38 MAPK or ERK1/2. On the other hand, a significant decrease in PKC activity, and inhibition of nuclear factor kappa B (NF-kB) translocation, were attributable to LC incubation. LC seems to counteract the pro-oxidative response to Ang II by modulating NADPH oxidase enzyme via reducing the activity of PKC and the translocation of NF-kB to the nucleus.

12. Collagen metabolic pathways

12.1 Cystine has a possible direct role in the regulation of α1(I) collagen mRNA.

Indication: patients with affected collagen metabolic pathway; patients with direct daily contact with toxic materials.
Related APIs: cystine.

Rishikof DC, et al. *Regulation of type I collagen mRNA in lung fibroblasts by cystine availability*. Biochem. J. 1998 331; 417–422.

Objective: to examine the requirements for individual amino acids on the regulation of α1(I) collagen mRNA.
Results: it was found that re-expression of α1(I) collagen mRNA was critically dependent on cystine but not on other amino acids. Following amino acid depletion, the addition of cystine with selective amino acids increased α1(I) collagen mRNA levels. The combination of glutamine and cystine increased α1(I) collagen mRNA levels 6.3-fold. Methionine or a branch-chain amino acid (leucine, isoleucine or valine) also acted in combination with cystine to increase α1(I) collagen mRNA expression, whereas other amino acids were not effective. The prolonged absence of cystine lowered steady-state levels of α1(I) collagen mRNA through a mechanism involving decreases in both the rate of gene transcription as assessed by nuclear run-on experiments and mRNA stability as assessed by half-life determination in the presence of actinomycin D.
Conclusion: the obtained data suggest that cystine directly affects the regulation of α1(I) collagen mRNA.

12.2 Higher silicon content in the hair is associated with a lower rate of hair loss.

Indication: patients with affected collagen metabolic pathway.
Related APIs: SiliciuMax™.

Araújo LA, et al. *Use of silicon for skin and hair care: an approach of chemical forms available and efficacy*. Biochem. J. 1998 331; 417–422.

On the skin, it is suggested that silicon is important for optimal collagen synthesis and activation of hydroxylating enzymes, improving skin strength and elasticity. Regarding hair benefits, it was suggested that a higher silicon content in the hair results in a lower rate of hair loss and increased brightness. For these beneficial effects, there is growing interest in scientific studies evaluating the efficacy and safety of using dietary supplements containing

silicon. Its use aims at increasing blood levels of this element and improving the skin and its annexes appearance. There are different forms of silicon supplements available and the most important consideration to be made in order to select the best option is related to safety and bioavailability. Silicon supplements are widely used, though there is wide variation in silicon bioavailability, ranging from values below 1% up to values close to 50%, depending on the chemical form.

13. Antioxidants

13.1 Continuous astaxanthin intake reduces oxidative stress.

Indication: smokers; patients undergoing a stressful period; patients with direct daily contact with toxic materials.
Related APIs: astaxanthin.

Chalyk NE, et al. *Continuous astaxanthin intake reduces oxidative stress and reverses age-related morphological changes of residual skin surface components in middle-aged volunteers*. Nutr Res. 2017 Dec; 48:40-48.

Objective: to analyze the effect of the continuous ingestion of carotenoid antioxidant astaxanthin (4 mg/d) for 4 weeks in residual skin surface components (RSSCs) morphology.
Methods: the study included 31 volunteers (17 men and 14 women) over the age of 40. RSSC samples were collected from the surface of the facial skin at the beginning (day 0) and end (day 29) of the study. In addition, blood samples were taken on days 0, 15, and 29 for measuring plasma levels of malondialdehyde that allowed assessing systemic oxidative stress.
Conclusion: results demonstrated that plasma malondialdehyde consistently decreased during astaxanthin consumption. The analysis of RSSC samples has revealed significantly decreased levels of corneocyte desquamation (P=0.0075) and microbial presence (P=0.0367) at the end of the study. The results demonstrated that continuous astaxanthin consumption produces a strong antioxidant effect resulting in facial skin rejuvenation which is especially pronounced in obese subjects.

13.2 Coenzyme-Q10 contains antioxidant properties.

Indication: smokers; patients undergoing a stressful period; patients with direct daily contact with toxic materials.
Related APIs: coenzyme-Q10.

Lance J, et al. *Coenzyme Q10--a therapeutic agent*. Medsurg Nurs. 2012 Nov-Dec;21(6):367-71.

Coenzyme Q10 (CoQ10) is critical to production of adenosine triphosphate and is an antioxidant that scavenges reactive oxygen species during oxidative stress. The use of CoQ10 in treating oxidative stress in cardiovascular diseases, diabetes and cancer was reviewed in this article.

13.3 Selenium antioxidant activity has been investigated for cancer chemoprevention, heart disease and immunity.

Indication: smokers; patients undergoing a stressful period; patients with direct daily contact with toxic materials.
Related APIs: selenium yeast.

Tinggi U, et al. *Selenium: its role as antioxidant in human health*. Environ Health Prev Med (2008) 13:102–108.

As an essential trace element, the importance of selenium (Se) in humans is well established, and its deficiency has caused serious health effects in humans, such as Keshan disease. Foods are major natural source of Se, and its levels generally depend on soil Se levels. Since its discovery as an important component of antioxidant enzymes, such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR) and iodothyronine deiodinases (IDD), there has been an increased interest in the study of other Se-containing proteins (selenoproteins) or enzymes (selenoenzymes). There are at least 30 selenoproteins that have been identified in mammals, and it has been estimated that humans have about 25 selenoproteins. The functional roles of some of these selenoproteins are still not fully understood, even though they have been conserved throughout evolution because of their unique physio-chemical properties. Because of their antioxidant activity, there has been a tremendous interest in the study of Se and its compounds in cancer chemoprevention, heart disease and immunity.

14. Antifungal

14.1 Coal tar therapy in dandruff and seborrheic dermatitis may be due antifungal activity.

Indication: patients with decreased response to glucocorticoids that require anti-inflammatory treatment due to a present pathology (psoriasis or seborrheic dermatitis).
Related APIs: coal tar.

Nenoff P, et al. *The Antifungal Activity of a Coal Tar Gel on Malassezia furfur in vitro*. Dermatology 1995;191:311-314.

Objective: to evaluate the antifungal activity of a coal tar gel on Malassezia furfur in vitro.
Methods: minimum inhibitory concentrations (MICs) of the tested agents were measured by agar dilution technique.
Conclusions: it is suggested that the effect of coal tar gel ointment in dandruff and seborrheic dermatitis therapy in vivo may be at least partly due to an antifungal activity of the coal tar.

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