

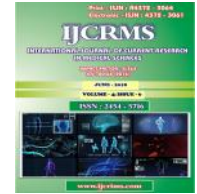


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A Review on Fibroid and Haptoglobin

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Abstract

Fibroids are a type of uterine leiomyoma. Fibroids grossly appear as round, well circumscribed (but not encapsulated), solid nodules that are white or tan, and show whorled appearance on histological section. Fibroids, particularly when small, may be entirely asymptomatic. Symptoms depend on the location and size of the fibroid. Important symptoms include abnormal uterine bleeding, heavy or painful periods, abdominal discomfort or floating, painful defecation, back ache, urinary frequency or retention, and in some cases, infertility. Haemoglobin is critical for life, providing cells with oxygen for their energy needs. However, outside of the confines of the erythrocytes (RBCs), haemoglobin is highly toxic. Its prosthetic group, haem, is lipophilic and readily intercalates into cell membranes to disrupt the lipid bilayers. Iron present in haem catalyzes the generation of ROS through the Fenton and Haber-Weiss reactions. Additionally, Hb avidly binds to nitric oxide, depleting the cell of a major modulator of vascular tone, resulting in changes in vasomotor: restriction and endothelial damage. The presence of free Hb is therefore a danger signal that is very rapidly attenuated by mechanisms that enable rapid and efficient removal of the protein in circulation or at the site of injury. Haptoglobin is ordered whenever a patient exhibits symptoms of anemia, such as pallor, fatigue, or shortness of breath, along with physical signs of hemolysis, such as jaundice or dark-colored urine. The test is also commonly ordered as a hemolytic anemia battery, which also includes a reticulocyte count and a peripheral blood smear. It can also be ordered along with a direct antiglobulin test when a patient is suspected of having a transfusion reaction or symptoms of autoimmune hemolytic anemia. Also, it may be ordered in conjunction with a bilirubin. A decrease in haptoglobin can support a diagnosis of hemolytic anemia, especially when correlated with a decreased red blood cell count, hemoglobin, and hematocrit, and also an increased reticulocyte count. This paper reviewed fibroid and haptoglobin.

Keywords: *Fibroid, Biomarkers, Haptoglobin, Haemoglobin*

Fibroid

Fibroids are a type of uterine leiomyoma. Fibroids grossly appear as round, well circumscribed (but not encapsulated), solid nodules that are white or tan, and show whorled appearance on histological section. The size varies, from microscopic to lesions of considerable size. Typically lesions the size of a grapefruit or bigger are felt by the patient herself through the abdominal wall ([1, 2]).

Microscopically, tumor cells resemble normal cells (elongated, spindle-shaped, with a cigar-shaped nucleus) and form bundles with different directions (whorled). These cells are uniform in size and shape, with scarce mitoses. There are three benign variants: bizarre (atypical); cellular; and mitotically active [3].

The appearance of prominent nucleoli with perinucleolar halos should alert the pathologist to investigate the possibility of the extremely rare hereditary leiomyomatosis and renal cell cancer (Reed) syndrome [3].

Signs and symptoms

Fibroids, particularly when small, may be entirely asymptomatic. Symptoms depend on the location and size of the fibroid. Important symptoms include abnormal uterine bleeding, heavy or painful periods, abdominal discomfort or floating, painful defecation, back ache, urinary frequency or retention, and in some cases, infertility. There may also be pain during intercourse, depending on the location of the fibroid. During pregnancy, they may also be the cause of miscarriage, bleeding, premature labor, or interference with the position of the fetus [3].

Pathogenesis

Fibroids are monoclonal tumors and approximately 40 to 50% show karyotypically detectable chromosomal abnormalities. When multiple fibroids are present they frequently have unrelated genetic defects. The exact cause of fibroids is not clearly understood, but the current working hypothesis is that genetic predispositions, prenatal hormone exposure and

the effects of hormones, growth factors and xenoestrogens cause fibroid growth. Known risk factors are African descent, obesity, polycystic ovary syndrome, diabetes, hypertension, and never having given birth [4].

It is believed that estrogen and progesterone have a mitogenic effect on leiomyoma cells and also act by influencing (directly and indirectly) a large number of growth factors, cytokines and apoptotic factors as well as other hormones. Furthermore, the actions of estrogen and progesterone are modulated by the cross-talk between estrogen, progesterone and prolactin signaling which controls the expression of the respective nuclear receptors. It is believed that estrogen promotes growth by up-regulating IGF-1, EGFR, TGF-beta1, TGF-beta3 and PDGF, and promotes aberrant survival of leiomyoma cells by down-regulating p53, increasing expression of the anti-apoptotic factor PCP4 and antagonizing PPAR-gamma signaling. Progesterone is thought to promote the growth of leiomyoma through up-regulating EGF, TGF-beta1 and TGF-beta3, and promotes survival through up-regulating Bcl-2 expression and down-regulating TNF-alpha. Progesterone is believed to counteract growth by downregulating IGF-1. Expression of transforming growth interacting factor (TGIF) is increased in leiomyoma compared with myometrium. TGIF is a potential repressor of TGF- pathways in myometrial cells [4].

While fibroids are common, they are not a typical cause for infertility, accounting for about 3% of reasons why a woman may not be able to have a child. The majority of women with uterine fibroids will have normal pregnancy outcomes. In cases of intercurrent uterine fibroids in infertility, a fibroid is typically located in a submucosal position and it is thought that this location may interfere with the function of the lining and the ability of the embryo to implant. Also, larger fibroids may distort or block the fallopian tubes [4].

Risk factors

The literature regarding predisposing risk factors for development of myomas should be interpreted

with caution. Analysis is limited by the paucity of studies available, the study populations (mostly in Caucasian women), and the conflicting results, suggests other unexamined factors may be involved. The high background prevalence of myomas, and possible detection bias as a consequence of increased medical surveillance of symptomatic women, may make interpretation of epidemiologic data difficult. The reliability of self-reported diagnoses may be questioned; the development of myomas may have preceded the exposure to risk factors but may not have been recognized until after presentation to a healthcare provider. Prospective, longitudinal studies are underway to better characterize the factors that influence the development of uterine myomas.

Types of fibroids

Fibroids can grow anywhere in the womb and vary in size considerably. Some can be the size of a pea, whereas others can be the size of a melon. The main types of fibroids are:

- **intramural fibroids** - the most common type of fibroid, which develop in the muscle wall of the womb
- **subserosal fibroids** - fibroids that develop outside the wall of the womb into the pelvis and can become very large
- **submucosal fibroids** - fibroids that develop in the muscle layer beneath the womb's inner lining and grow into the cavity of the womb. In some cases, subserosal or submucosal fibroids are attached to the womb with a narrow stalk of tissue. These are known as pedunculated fibroids [2].

Causes and risk factors

Uterine fibroids develop from the smooth muscle of the myometrium. A single cell reproduces repeatedly, eventually creating a pale, firm, rubbery mass. Medical research is working to identify the cause of fibroids, but some contributing factors are evident:

- Genetic alterations are found in replicating uterine muscle cells.
- Hormones estrogen and progesterone influence the growth of Fibroids; fibroids have an

increased number of estrogen receptors compared to normal uterine tissue

- Other chemicals such as growth factors and cytokines interact with tissue and promote the growth of fibroids

Risk of developing uterine fibroids also increases with other factors:

- Family history of fibroids
- Obesity
- African-American women have a higher risk to get fibroids larger in size and at an earlier age than other women
- Oral contraceptives, pregnancy and childbirth have been shown to have protective effects against uterine fibroids

Symptoms of uterine fibroid

Uterine fibroid symptoms can emerge slowly over years or rapidly in several months. Most women with uterine fibroids show mild or no symptoms and do not require treatment. Symptoms can pose a problem for some, and the location of the fibroid usually influences the types of symptoms present. The most common symptoms include:

- Heavy menstrual bleeding
- Menstrual periods lasting longer than normal (7+ days)
- Pelvic pain or pressure
- Frequent urination
- Constipation
- Lower back or leg pain [2].

Uterine fibroid complications and prognosis

Uterine fibroids can cause multiple complications with pregnancy but it is not common. Sometimes, fibroids can make it difficult to become pregnant, creating infertility. During pregnancy, existing fibroids may grow due to the increased blood flow and estrogen levels. Large fibroids in the uterine cavity can cause abnormal fetal positions and placenta problems. If fibroids block the birth canal then a cesarean section delivery may be necessary. Uterine fibroids increase the risk for miscarriage, and premature labor and delivery.

Pain and excessive bleeding after childbirth are also seen. Other complications of fibroids include:

- Severe pain and excessive bleeding, which may require surgery
- Anemia resulting from heavy bleeding
- Urinary tract infections resulting from blockage of the urinary tract if a fibroid presses on it
- Infection or breakdown of uterine fibroid tissue

Diagnosis

While palpation used in a pelvic examination can typically identify the presence of larger fibroids, gynecologic ultrasonography (ultrasound) has evolved as the standard tool to evaluate the uterus for fibroids. Sonography will depict the fibroids as focal masses with a heterogeneous texture, which usually cause shadowing of the ultrasound beam. The location can be determined and dimensions of the lesion measured. Also magnetic resonance imaging (MRI) can be used to define the depiction of the size and location of the fibroids within the uterus. Imaging modalities cannot clearly distinguish between the benign uterine leiomyoma and the malignant uterine leiomyosarcoma, however, the latter is quite rare. Fast growth or unexpected growth, such as enlargement of a lesion after menopause; raise the level of suspicion that the lesion might be a sarcoma. Also, with advanced malignant lesions there may be evidence of local invasion. Biopsy is rarely performed and if performed, is rarely diagnostic. Should there be an uncertain diagnosis after ultrasounds and MRI imaging, surgery is generally indicated [2].

Chemical pathology of fibroid

Biomarkers are sought to provide diagnostic as well as prognostic information. Ideally, a good biomarker must be both reliable and reproducible. They must be easily measured in peripheral tissues or bodily fluids. A biomarker should be sensitive and specific; it should be cheap, and should detect a potentially morbid for which there is a useful intervention. The development of biomarkers for leiomyomas would provide

substantial cost savings, as they are easily accessible from the peripheral vasculature [5].

Prolactin

Prolactin is a protein hormone involved in a variety of mammalian physiologic actions such as lactogenesis. Prolactin mediates its function by interacting with type-1 cytokine receptors, and signals through Janus kinase, signal transducers, and activators of transcription (JAK/STAT) pathways. Although isolated as a pituitary hormone, prolactin is expressed in other tissues including uterine leiomyomas. A study found that serum prolactin in patients with uterine fibroids before myomectomy or hysterectomy was elevated (169.64 ± 133.1 ng/mL) compared with postoperative levels (19.69 ± 9.54) ($P < .05$) and controls. The investigators considered a prolactin level >35 ng/mL to be elevated; despite having 84% of patients with uterine leiomyomas meet this criteria, they did not evaluate any other etiologies of hyperprolactinemia [5].

Total Protein

The total protein serum test measures the total amount of albumin and globulin in the blood. Values below the normal threshold usually are associated with nutritional deficiency, liver and kidney disease, or prolonged hemorrhage or anemia. Elevated total protein values can be a marker of chronic inflammation or malignancies such as multiple myeloma. In a prospective trial examining total protein as a biomarker for uterine leiomyomas, the serum total protein level was lower in patients with uterine fibroids before they underwent hysterectomy for leiomyomas or myomectomy. The preoperative serum total protein levels were statistically significantly lower in patients with fibroids (5.56 ± 9.66 g/dL) and – returned to levels similar to fibroid- free controls 3 weeks after surgery (6.83 ± 0.9 g/dL). However, as patients with fibroids are predisposed to abnormal uterine bleeding and menorrhagia, it is possible that the reduced serum total protein demonstrated in patients with leiomyoma was a result of abnormal, heavier uterine bleeding versus the fibroids themselves [5].

Soluble Serum HLA-G

Human leukocyte antigen G (HLA-G) is a regulatory antigen of the immune system. Expressed in the uterus and originally demonstrated in the cytotrophoblast, HLA-G has been demonstrated to be elevated in ovarian carcinoma and other; cancers such as melanoma and breast carcinoma, in addition to peritoneal inflammatory conditions such as endometriosis.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is an angiogenic peptide that has been shown to be critical for the growth of numerous tumors. Chen et al. evaluated serum VEGF levels in women with uterine leiomyomas as a prospective biomarker. Expression of VEGF was increased in uterine fibroids compared with adjacent myometrium. The investigators conducted a prospective trial evaluating VEGF in 80 women before and after hysterectomy for symptomatic fibroids. The serum VEGF levels did not correlate with uterine weight, which was used as a surrogate marker of fibroid burden, or the number of fibroids. However, serum VEGF levels declined after hysterectomy from 716.3 ± 457.99 to 581.81 ± 403.32 ($P < 0.5$). This, however, was not a novel finding, as it was previously demonstrated that the uterus itself is an important source of VEGF production. The investigators concluded rightly that serum VEGF levels did not predict uterine fibroid development, and it is not an effective biomarker for uterine leiomyoma [5].

Ghrelin and Obestatin

Ghrelin is a 28 amino acid peptide, secreted mainly in the stomach, which primarily functions in control of energy homeostasis. To be active, ghrelin requires N-octanoylation at serine 3. Ghrelin and its receptors have been expressed in hormone-dependent tumors, uteri, and many other organs. In addition, ghrelin has been shown to be involved in steroidogenesis and cellular leiomyomas. Obestatin originates from the ghrelin prohormone and is secreted by the stomach. In contrast of ghrelin, obestatin acts as

an anorectic hormone, has been implicated in cellular proliferation, and exhibits other proliferative effects, such as increasing phosphorylation of certain response elements and activation of growth factor [5].

Lactate Dehydrogenase A (LDHA)

Lactate dehydrogenase A (LDHA), which is involved in anaerobic glycolysis, converts pyruvate to lactate under anaerobic conditions. Its serum levels are often increased in cancer patients. The gene of LDHA is often up-regulated and has been linked to poor prognosis in various cancers. When evaluating 24 patients with leiomyomas compared with controls, Koukourakis et al demonstrated that the patients with fibroids had statistically significantly higher serum LDHA levels (310 ± 81 vs. 256 ± 68 ; $P = .05$). However, this analysis was conducted along with end ovarian cancer, making this a poor differentiator of leiomyoma from coexisting malignancy. In addition, LDH is a marker of anaerobic metabolism and will be influenced by a variety of benign and malignant conditions that influence metabolic conditions, making it unusable in the diagnosis and follow-up observation of uterine leiomyoma [5].

Hypermethylated Death-Associated Protein Kinase (DAPK)

Aberrant DNA methylation has been previously found in uterine leiomyomas when compared with matched myometrium.

Cancer Antigen-125

Cancer antigen 125 (CA125) is a marker of nonspecific peritoneal conditions and is not specific to ovarian malignancy. In a study of 55 patients with leiomyomas or adenomyosis, CA125 levels were 102.1 kIU/L, 34.6 kIU/L, and 33.1 kIU/L in adenomyosis, leiomyomas, and controls, respectively. The CA125-positive rates (defined as >50 kIU/L) were 80%, 10%, and 5%, respectively. In a study of tumor biomarkers, 92% of women with leiomyomas demonstrated elevated tumor markers such as elevated CA125 or CA19-9 (>40 TU/mL).

Studies have assessed CA125 for its utility in preoperative diagnosis of uterine sarcoma. In a retrospective study of 2,382 patients undergoing surgery for uterine leiomyoma, 26 patients were diagnosed with sarcoma. The preoperative CA125 levels were not predictive of sarcoma. Another study assessed the potential role of preoperative serum CA125 for the differential diagnosis between uterine leiomyoma and leiomyosarcoma in 42 patients and 84 controls with benign pathology [5].

Hematopoietic Growth Factors

Hematopoietic growth factors—macrophage colony-stimulating factor (M-CSF) and granulocyte colony-stimulating factor (G-CSF)—were investigated as serum markers in patients with endometrial cancer (n = 55), women with uterine myomas (n= 30), and healthy controls. Both were noted to be higher in women with leiomyomas when compared with the control group. The investigators suggested that M-CSF could be particularly useful in distinguishing endometrial cancer and leiomyomas. However, the sensitivity of hematopoietic growth factors for recognition of uterine leiomyomas was poor at only 51%. When CA125 was included as an additional marker, the specificity approached 93% [5].

Human Epididymis Protein 4 (HE4)

Human epididymis protein 4 (HE4) has been shown to be a promising biomarker in ovarian cancer, with improved sensitivity and specificity over CA125 in recognition of malignant pelvic masses. It is a protein initially isolated from epithelial cells in the human epididymis and is expressed throughout the body, including in the female reproductive organs. Moore et al. evaluated serum levels of HE 4 and CA125 in over 1,000 premenopausal and postmenopausal women with benign pelvic disease. Of 61 patients with leiomyomas, only three patients (5%) and an HE4 level greater than the 95th percentile. Comparatively, 26% of patients with fibroids were found to have an elevated serum CA125. This study concluded that HE4 is elevated less frequently than CA125 in benign gynecologic

diseases, including uterine leiomyomas, which provides the basis for its use as a biomarker for ovarian neoplasia.

Proteomics

Initial work in proteomics has been performed to identify plasma proteins as biomarkers for diagnosing uterine fibroids used two-dimensional differential gel electrophoresis to identify differentially expressed proteins in the plasma of patients with and without uterine leiomyomas. The differentially expressed proteins were then identified by matrix-assisted laser ionization mass spectrometry. The results yielded 20 differentially expressed plasma proteins, the majority belonging to either coagulation or transportation groups with cytoskeleton, inflammatory cascade, and signal transduction proteins also being differentially expressed. The serum proteins with the highest differential expression ratios were actin, fibrinogen, gelsolin, and serotransferrin. Gelsolin is a regulator of actin assembly [5].

Gonadal Hormones and Growth Factors

There is evidence to support that gonadal hormones and growth factors are responsible for leiomyoma growth. To evaluate whether women with fibroids demonstrate higher steroid hormone and growth factor serum levels, 51 women with leiomyomas of >14 weeks' size were compared with 30 control fibroid-free patients. The levels of plasma insulin-like growth factor I (IGF-1) in women with leiomyomas during the follicular and luteal phases were almost identical to those if fibroid-free women. Furthermore, estrone, estradiol, and progesterone were measured repeatedly in each group during both the follicular and luteal phases of the menstrual cycle and were similar in both groups.

Haematology of fibroid

Not much research data is available on the haematological profile of leiomyomata patients. Analysis of collected data however showed a significant difference between the red cell indices of the patients and the controls. The patients had higher mean values of all red cell indices, except

MCV, compared to the controls contrary to popular reasoning that menorrhagia, a common symptom in fibroid patients, should reduce the red cell indices of the patients. Erythrocytosis has been commonly used to describe this phenomenon instead of polycythaemia since there is only the elevation of the erythrocytes and not the pancytosis that characterizes polycythaemia [6]. From the data obtained the red blood cell count and the associated red cell indices were the haematologic parameters that differed significantly between the patients and the controls. Three schools of thought have emerged as possible causes of the erythrocytosis, all based on the observation that there is complete resolution of the erythrocytosis after surgical extirpation of the leiomyomata. Some authors proposed intrauterine shunting as the reason behind the erythrocytosis. Their theory about the existence of intra-myomatous arteriovenous shunts is supported by histopathologic findings of marked vascularity and sinusoidal vascular spaces. These shunts allow the flow of nonoxygenated blood; the arterial vasculature, stimulating the bone marrow to increase red cell auction [6].

Haptoglobin as a diagnostic tool

Haptoglobin, in its simplest form, consists of two alpha and two beta chains, connected by disulfide bridges. The chains originate from a common precursor protein, which is proteolytically cleaved during protein synthesis. Hp exists in two allelic forms in the human population, so-called *Hp1* and *Hp2*, the latter one having arisen due to the partial duplication of *Hp1* gene. Three genotypes of Hp, therefore, are found in humans: Hp1-1, Hp2-1, and Hp2-2. Hp of different genotypes has been shown to bind hemoglobin with different affinities, with Hp2-2 being the weakest binder [7].

Synthesis of haptoglobin

Haptoglobin is produced mostly by hepatocytes but also by other tissues such as skin, lung and kidney. In addition, the haptoglobin gene is expressed in murine and human adipose tissue. Haptoglobin had been shown to be expressed in adipose tissue of cattle as well [6].

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Hp has been found in all mammals studied so far, some birds, e.g., cormorant and osrich but also, in its simpler form, in bony fish, e.g., zebrafish. It is interesting to note that Hp is absent in at least some amphibians (*Xenopus*) and neognathous birds (chicken and goose).

Function

This gene encodes a preproprotein that is processed to yield both alpha and beta chains, which subsequently combines as a tetramer to produce haptoglobin. Hp Haptoglobin functions to bind free plasma hemoglobin, which allows degradative enzymes to gain access to the hemoglobin while at the same time preventing loss of iron through the kidneys and protecting the kidneys from damage by hemoglobin. For this reason, it is often referred to as the suicide protein [7].

Antioxidant/anti-inflammatory role

Under conditions of compromised oxygen supply, such as occurs in injury, infection or malignancy, oxygen species with free unpaired electrons are generated during mitochondrial electron transport. Referred to as highly reactive oxygen species (ROS), their production causes damage to cell membranes and macromolecules (lipids, proteins and DNA). In addition, cells of the immune system generating ROS also produce reactive nitrogen species (RNS), for example peroxynitrite (ONOO⁻) by the interaction between nitric oxide and superoxide,

which are equally damaging to cell membranes and DNA. Cellular non-enzymatic antioxidants, which include vitamin C, vitamin E, glutathione and others, maintain cellular redox homeostasis in order to prevent or Control cellular damage in the event of an inflammatory response. Hp possesses an innate phenotype-dependent antioxidant activity that exceeds by far that of vitamin C (ascorbic acid) and contributes significantly to this process, particularly at extravascular sites. Both in vitro and in vivo studies have established that subjects with the Hpl-1 phenotype are more likely to resist cellular oxidative stress than those with the Hp2-2 phenotype, with Hp2-1 being intermediate.

Haptoglobin binding

Haemoglobin is critical for life, providing cells with oxygen for their energy needs. However, outside of the confines of the erythrocytes (RBCs), haemoglobin is highly toxic. Its prosthetic group, haem, is lipophilic and readily intercalates into cell membranes to disrupt the lipid bilayers. Iron present in haem catalyzes the generation of ROS through the Fenton and Haber-Weiss reactions. Additionally, Hb avidly binds to nitric oxide, depleting the cell of a major modulator of vascular tone, resulting in changes in vasomotor: restriction and endothelial damage. The presence of free Hb is therefore a danger signal that is very rapidly attenuated by mechanisms that enable rapid and efficient removal of the protein in circulation or at the site of injury.

Clinical significance

Mutations in this gene or its regulatory regions cause ahaptoglobinemia or -hypohaptoglobinemia. This gene has also been linked to diabetic nephropathy, the incidence of coronary artery disease in type 1 diabetes, Crohn's disease, inflammatory disease behavior, primary sclerosing cholangitis, susceptibility to idiopathic Parkinson's disease, and a reduced incidence of *Plasmodium falciparum malaria* [6]. Since the reticuloendothelial system will remove the haptoglobin-hemoglobin complex from the body, haptoglobin levels will be decreased

in hemolytic anemias. In the process of binding hemoglobin, haptoglobin sequesters the iron within hemoglobin, preventing iron-utilizing bacteria from benefiting from hemolysis. It is theorized that, because of this, haptoglobin has evolved into an acute-phase protein. HP has a protective influence on the hemolytic kidney. Some studies associate certain haptoglobin phenotypes with the risk of developing schizophrenia.

Haptoglobin is ordered whenever a patient exhibits symptoms of anemia, such as pallor, fatigue, or shortness of breath, along with physical signs of hemolysis, such as jaundice or dark-colored urine. The test is also commonly ordered as a hemolytic anemia battery, which also includes a reticulocyte count and a peripheral blood smear. It can also be ordered along with a direct antiglobulin test when a patient is suspected of having a transfusion reaction or symptoms of autoimmune hemolytic anemia. Also, it may be ordered in conjunction with a bilirubin. A decrease in haptoglobin can support a diagnosis of hemolytic anemia, especially when correlated with a decreased red blood cell count, hemoglobin, and hematocrit, and also an increased reticulocyte count [6].

If the reticulocyte count is increased, but the haptoglobin level is normal, this may indicate that cellular destruction is occurring in the spleen and liver, which may indicate a drug-induced hemolysis, or a red cell dysplasia. The spleen and liver recognize an error in the red cells (either drug coating the red cell membrane or a dysfunctional red cell membrane), and destroy the cell. This type of destruction does not release hemoglobin into the peripheral blood, so the haptoglobin cannot bind to it. Thus, the haptoglobin will stay normal if the hemolysis is not severe. In severe extra-vascular hemolysis, haptoglobin levels can also be low, when large amount of hemoglobin in the reticuloendothelial system leads to transfer of free hemoglobin into plasma.

If there are symptoms of anemia but both the reticulocyte count and the haptoglobin level are normal, the anemia is most likely not due to

hemolysis, but instead some other error in cellular production, such as aplastic anemia Haptoglobin levels that are decreased but do not accompany signs of anemia may indicate liver damage, as the liver is not producing enough haptoglobin to begin with [6].

Haptoglobin and fibroid

Haptoglobin is indeed an acute-phase protein, any inflammatory process (infection, extreme stress, burns, major crush injury, allergy, etc.) may increase the levels of plasma haptoglobin.

Inflammation is involved in reproductive events such as ovulation, menstruation and implantation. Regulation and resolution of inflammatory pathways is necessary for proper reproductive function, and the onset of reproductive disorders may be the result of malfunctioned or persistent inflammation. The commonality of fibroids and the universality of menstruation has led to an increasing belief that injury related to menses may cause an improper inflammatory response leading to the formation of uterine fibroids [7].

Uterine fibroids grow from the smooth muscle and can be found on the peritoneum, within the myometrium and on the endometrium. These fibroids are non-cancerous growths which often develop during childbearing years, after a woman has gone through puberty. Although the exact cause is unknown, it appears that the hormone estrogen, which helps regulate the menstrual cycle, plays a key role in their growth [7].

Haptoglobin and infection

According to Delanghe *et al.* [8] Patients infected with HIV-1 and with Hp2-2 phenotype have a worse prognosis, related to a more rapid rate of viral replication, than HIV-1 infected patients with the Hp1-1 phenotype. Hp2-2 patients also show higher iron levels and oxidize more vitamin C. It is possible that the less efficient protection against heme-driven oxidative stress by Hp2-2 may stimulate the viral replication.

Haptoglobin and cancer

High amounts of Hp in plasma and locally in tumoral tissue have been observed in diverse types of malignancies including, lung, bladder, breast cancer, leukemia, glioblastoma, malignant lymphoma, and ovarian can [9]. The suggested functions of Hp in cancer are as a biomarker of malignancy, as a -regulator of the immune response against tumor cells, and as a facilitator of metastasis, since Hp seems to participate in cell migration and angiogenesis [10].

Hapoglobin and atherosclerosis

In cross sectional studies, the Hp2-2 phenotype is also associated with an increased risk of atherosclerotic vascular disease and acute myocardial infarction. The lower antioxidant capacity of Hp2-2 together with a lower capacity of Hp2-2 in stimulating macrophages to secrete anti-inflammatory cytokines after binding CD163, might be the reason why individuals with Hp2-2 phenotype are more susceptible for cardiovascular diseases [11].

Haptoglobin and Myasthenia gravis

High serum levels of Hp have been found in patients with myasthenia gravis. Hp serum level is directly correlated with the severity of the disease. This correlation is explained by the presence of high levels of pro-inflammatory cytokines during active disease. To determine the Hp serum levels in patients with myasthenia can be useful to monitor the severity of the disease [12].

Haptoglobin and Arthritis

In patients with active rheumatoid arthritis, high serum levels of Hp have been found. Levels of Hp correlate with clinical disease activity [13]. In juvenile idiopathic arthritis (JIA), a heterogeneous group of inflammatory diseases, Hp was found in inflamed joints. Hp was locally produced in synovial fluid of patients with JIA. Moreover, Hp was expressed differentially between JIA subtypes. Hp expression was increased in systemic JIA, The presence of Hp in the inflamed tissue suggests that Hp plays a role in the

progression and pathology of the disease and can also be used as a biomarker of disease activity [14].

Haptoglobin and Psoriasis

In psoriasis, a structure modification of Hp was described that might impair the Hb binding function and also the activity of the lecithin-cholesterol acyltransferase (LCTA) enzyme [15]. The structural modification of Hp in psoriasis patients is an abundance or structure change of specific glycans that differ or do not exist in Hp from healthy donors. These changes are associated with altered function of that might have an impact on the disease activity. Interestingly, it was found that there is no higher prevalence of any of the three phenotypes of Hp in psoriasis [16].

Haptoglobin and Lupus

It has been shown that in systemic lupus erythematosus (SLE) patients, Hp plasma levels correlate with severity of the disease and that the Hp2-2 phenotype is over-represented in SLE patients. The association of the Hp2-2 phenotype with SLE can have several implications. SLE I is an autoimmune disease mediated by B cells that secrete self-reactive pathogenic antibodies. Individuals with the Hp2-2 phenotype seem to have a higher number of CD22 binding sites compared to other Hp phenotypes. Additionally, it is known that cardiovascular disease is a common complication of SLE. The finding that Hp2-2 has lower anti-oxidant capacity [17].

Haptoglobin and Celiac disease

The frequency of the Hp2-2 phenotype in celiac disease patients has been reported to be higher than in the general population. However, Hp2-2 phenotype was associated with a more severe clinical course of the disease [18]. The structural differences and the functional differences between Hp phenotypes may account for phenotype association of Hp to the more severe form of celiac disease. Hp2-2-Hb complexes upon binding CD 163 induce lower expression of IL-10 compared to Hp1-1-Mb complexes. Hp2-2 is as

well associated to a stronger immune response [19].

Haptoglobin and Type I diabetes

In patients with a long duration of type I diabetes, an increased risk of cardiovascular disease was observed in patients with the Hp2-2 phenotype. Again, Hp2-2 has low antioxidant capacity and a low efficiency in preventing haeme release; this can contribute to the higher cardiovascular risk in type I diabetes. Also, it was shown that the Hp phenotype may be an independent determinant of early renal function decline and progression to end stage renal disease [20].

Haptoglobin and inflammatory bowel diseases (IBD)

Inflammatory bowel disease (IBD) is a chronic, relapsing intestinal inflammatory condition that is classified into two major forms, Crohn's disease (CD) and ulcerative colitis (UC). The etiology is unknown, but the pathogenesis is likely dependent on the interaction between local immune reaction and environmental factors in susceptible individuals. To explore a possible role of Hp in IBD patients we recently studied polymorphisms in the Hp locus in a cohort of CD and UC patients. It was found that the Hp2 locus was overrepresented in CD and UC patients compared to healthy individuals. These results indicate that Hp phenotype can be a risk factor for IBD. Since Hp phenotypes differ in their function, further research is necessary to understand how Hp genotype modulates IBD pathogenesis.

Conclusion

Fibroids are a type of uterine leiomyoma. Fibroids grossly appear as round, well circumscribed, solid nodules that are white or tan, and show whorled appearance on histological section. Fibroids, particularly when small, may be entirely asymptomatic. Symptoms depend on the location and size of the fibroid. Important symptoms include abnormal uterine bleeding, heavy or painful periods, abdominal discomfort or floating, painful defecation, back ache, urinary frequency or retention, and in some cases, infertility.

The presence of free haemoglobin is therefore a danger signal that is very rapidly attenuated by mechanisms that enable rapid and efficient removal of the protein in circulation or at the site of injury by haptoglobin. Haptoglobin is ordered whenever a patient exhibits symptoms of anemia, such as pallor, fatigue, or shortness of breath, along with physical signs of hemolysis, such as jaundice or dark-colored urine. A decrease in haptoglobin can support a diagnosis of hemolytic anemia, especially when correlated with a decreased red blood cell count, hemoglobin, and hematocrit, and also an increased reticulocyte count.

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