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Recent Advances on Sex Hormone-Binding Globulin Regulation by Nutritional Factors: Clinical Implications

*Laura Brianso-Llort, Cristina Saéz-Lopez, Anna Alvarez-Guaita, Lorena Ramos-Perez, Cristina Hernandez, Rafael Simó, and David M. Selva**

Sex hormone-binding globulin (SHBG) is a homodimeric glycoprotein produced by the human liver and secreted into the systemic circulation where it binds with high affinity sex steroids regulating their availability in blood and accessibility to target tissues. Plasma SHBG levels are altered in metabolic disorders such as obesity, anorexia, and insulin resistance. Several reports have shown that diets in terms of total calories or fat, fiber, or protein content can alter plasma SHBG levels. However, there are many components in a diet that can affect *SHBG* gene expression in the liver. In order to unravel the molecular mechanisms by which diets regulate SHBG production, it would be necessary to analyze single diet components and/or nutritional factors. This review summarizes the recent advances in identifying different nutritional factors regulating SHBG production and the related molecular mechanism, as well as the clinical implications.

1. Sex Hormone-Binding Globulin Background

1.1. Human Sex Hormone-Binding Globulin Gene

The human *SHBG* gene is located on chromosome 17p13.1 and it spans up to 11-kb containing two known transcription units: a) first transcription unit or proximal promoter (4.3-kb) that is responsible for driving the expression of the *SHBG* gene in the hepatocytes that secrete SHBG protein into the circulation[1]; b) second transcription unit containing an alternative promoter which drives the expression of the *SHBG* gene in germ cells of the testes producing a smaller isoform than the plasmatic SHBG that accumulates in the acrosome of human sperm[1] (**Figure 1**).

L. Brianso-Llort, C. Saéz-Lopez, A. Alvarez-Guaita, L. Ramos-Perez, C. Hernandez, R. Simó, D. M. Selva
Diabetes and Metabolism Research Unit
Vall Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona and Biomedical Network Research Centre on Diabetes and Metabolic Diseases (CIBERDEM, ISCIII)
Barcelona 08035, Spain
E-mail: david.martinez.selva@vhir.org

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1.2. Transcription Factors Regulating Hepatic SHBG Gene Expression

The human *SHBG* proximal promoter is a TATA-less promoter that contains different footprint (FP) regions which have been well characterized during the last decade (Figure 1):

- FP1 region: chicken ovalbumin upstream promoter transcription factor (COUP-TFI) and hepatocyte nuclear factor 4 alpha (HNF-4α), which represses and activates SHBG transcription, respectively.[2]
- FP3 region: HNF-4α, estrogen receptor alpha (ERα), and constitutive androstane receptor (CAR) activate SHBG transcription, while peroxisome proliferator activated receptor gamma (PPARγ) inhibits SHBG transcription.[2,3]
- FP4 region: upstream stimulatory factor 1/2 (USF1/2) activates SHBG transcription.[4]

1.3. SHBG Function and Role as Biomarker of Metabolic Disturbances

SHBG is a glycoprotein produced by the human liver and secreted into the circulation where it binds with high affinity both androgens and estrogens regulating their availability in blood and accessibility to target tissues and cells.[5] The plasma SHBG levels are altered in different metabolic disorders, in fact low plasma SHBG are inversely associated with metabolic syndrome, insulin resistance, obesity, type 2 diabetes, and gestational diabetes.[6–8] There are also emerging evidences that low SHBG levels could represent an independent biomarker of proinflammatory states and SHBG levels may be an indicator of low-grade inflammation in obese individuals.[9] In addition, low SHBG is associated with a greater coronary artery calcium score and increased risk for cardiovascular disease (CVD) in postmenopausal women.[10–14] Plasma SHBG levels correlate with the body mass index (BMI) and subjects living with obesity and anorexia have low and high plasma SHBG, respectively.[12–14] Moreover, it has been also suggested that determining plasma SHBG levels could be a reliable index of nutritional status in anorexia[13] (**Figure 2**).

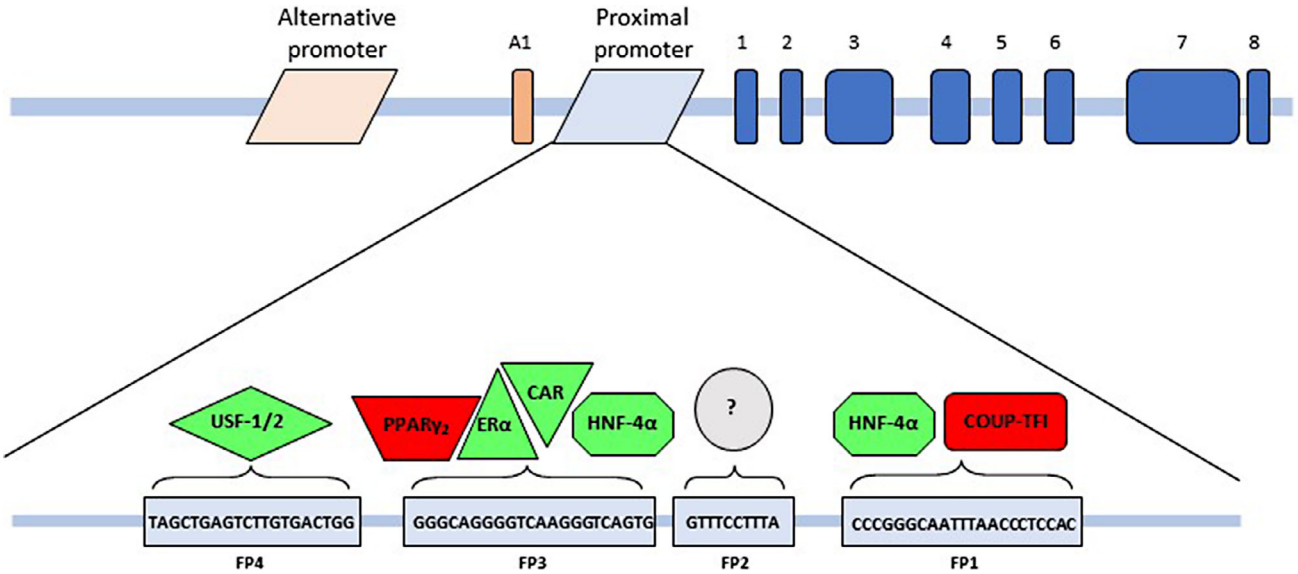

Figure 1. Human *SHBG* gene structure and transcription factors regulating its expression. The hepatic expression of SHBG is driven by a proximal promoter resulting in an mRNA that comprises eight exons. The SHBG alternative promoter is expressed in testicular germ cells resulting in an mRNA that comprises an alternative exon 1 (A1) followed by exons 2–8. The proximal *SHBG* promoter has been well characterized and several transcription binding sites (footprint regions) and its transcription factors binding them have been identified.

1.4. Dietary Composition and SHBG

Several studies had explored the relation between SHBG plasma levels and the dietary composition in terms of fiber, fat, and protein content, as well as total calories. However, the conclusions of these reports are sometimes unclear or conflicting.

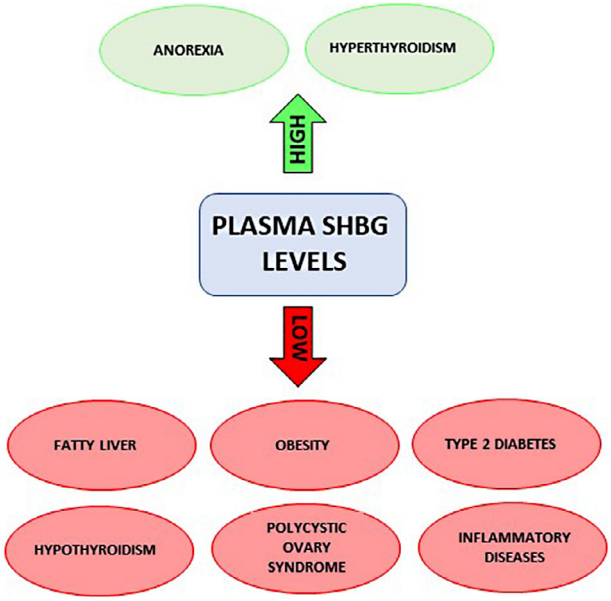

Figure 2. Altered plasma SHBG levels can be found in several human diseases. Subjects suffering from fatty liver disease, obesity, type 2 diabetes, hypothyroidism, polycystic ovary syndrome, or inflammatory diseases are characterized by having low plasma SHBG levels. On the contrary, subjects suffering from anorexia or hyperthyroidism have high plasma SHBG levels.

- Fiber: Several studies have shown that women under high fiber diets had decreased plasma SHBG levels,[15,16] whereas others reported that vegetarians had an increase in plasma SHBG levels compared to nonvegetarians.[16–18]
- Fat: It has been suggested that fat intake may be related to SHBG levels.[19,20] A study by Reed et al.[21] showed that men fed a high-fat diet had a decrease in plasma SHBG levels, while men fed a low-fat diet had an increase in plasma SHBG levels.
- Protein: A report by Vermuelen et al. described that a high protein diet increased plasma SHBG levels.[22]
- Total calorie consumption: Studies have shown that women suffering from anorexia had a significant decrease in plasma SHBG levels after increasing their total calorie intake,[23] whereas women suffering from polycystic ovary syndrome showed an increase in plasma SHBG levels when fed a very low-calorie diet.[24]

The discrepancies between reports in humans regarding the effects of different diets on SHBG regulation may be due to the fact that there are many components in these diets that can vary between studies and affect different *SHBG* gene expression in the liver. In order to understand the molecular mechanisms by which different diets regulate SHBG production, it would be necessary to analyze single diet components and/or nutritional factors to determine the associated molecular mechanisms.

2. SHBG Regulation by Nutritional Factors and Associated Molecular Mechanisms

In recent years, several advances of importance have been made in terms of identifying several nutritional factors regulating SHBG production and the related molecular mechanism using in vitro and in vivo approaches as well as clinical studies. Specifically, a) high carbohydrate diets (glucose and fructose)

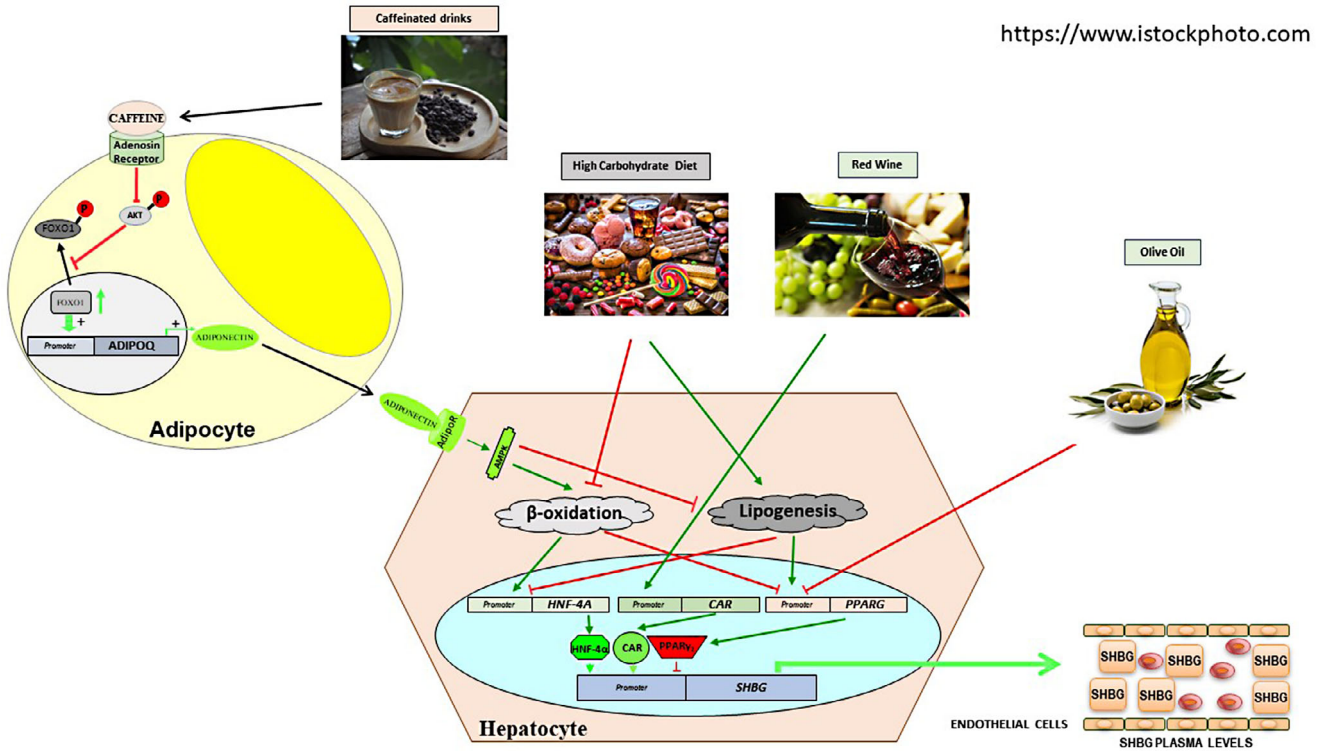

Figure 3. Molecular mechanisms by which caffeine, high carbohydrate diets, red wine, and olive oil regulate SHBG expression. Caffeine upregulates hepatic SHBG expression by increasing adiponectin production through AKT/FOXO1 pathway in the adipose tissue, adiponectin actions in the liver include the increase of β-oxidation and the decrease of lipogenesis which in turn increases HNF-4α and decreases PPARγ resulting in an increase SHBG expression. High carbohydrate diets decrease β-oxidation and the increases lipogenesis which in turn decreases HNF-4α and increases PPARγ resulting in an inhibition of SHBG expression. Red wine and olive oil increase SHBG expression by increasing CAR protein levels and decreasing PPARγ protein levels, respectively.

have been shown to reduce SHBG production by increasing hepatic lipogenesis and therefore hepatic lipid content; b) components of Mediterranean diet such as olive oil and red wine have been shown to increase hepatic SHBG production by different mechanisms through specific transcription factors; c) caffeine consumption have been demonstrated to increase hepatic SHBG production indirectly by acting in the adipose tissue (**Figure 3**).

2.1. Carbohydrates

It is well known that higher intake of sugar and sugar-sweetened beverages are associated with lower plasma SHBG levels.[25] In addition, it has been shown that high carbohydrate diets, fructose in particular, induce hepatic de novo lipogenesis and inhibit mitochondrial β-oxidation, resulting in intrahepatic lipid accumulation.[26,27] In this regard, we have demonstrated in in vitro experiments using HepG2 cells that monosaccharides directly regulate *SHBG* gene expression in these cells by increasing de novo lipogenesis.[28] Mechanistically, the increase in hepatic lipogenesis and lipid accumulation induces an upregulation of the peroxisome proliferator activated receptor gamma (PPARγ) and a decrease of the hepatocyte nuclear factor alpha (HNF-4a) levels, which are the main transcription factors inhibiting and activating *SHBG* gene expression respectively, resulting in a decrease in SHBG expression and production.[2,28,29] These findings were further corroborated by treating HepG2 cells with monosaccharides in the presence of cerulenin, a fatty acid synthase inhibitor. Cerulenin was able to inhibit the monosaccharide-induced reduction of SHBG production in HepG2 cells.[28] In addition, these results were corroborated in in vivo studies using the humanized *SHBG* transgenic mice fed with high amounts of sucrose, glucose, or fructose. Under these conditions, the human *SHBG* transgenic mice showed decreased plasma SHBG levels.[28] It is important to mention that fructose was more effective in reducing SHBG plasma levels than glucose or sucrose.[28] The explanation is that unlike glucose, ingested fructose is preferentially metabolized by the liver[30] and this and other features make it an exceptionally lipogenic sugar.[31–33] In this regard, it has been shown that hepatic lipogenesis is strongly associated with fatty liver in humans.[34] Norbert et al. showed that elevated liver fat content strongly correlated with circulating SHBG in humans.[35] In a subsequent study, Peter et al. replicate these findings in an independent group of subjects and found that besides age and sex, liver fat content, but not total body or visceral fat, was an independent predictor of plasma SHBG levels.[36] The authors also found using data from a longitudinal lifestyle intervention study, that subjects having the largest increase in SHBG plasma levels were those showing the largest decrease in liver fat. Moreover, an inverse correlation was found between SHBG mRNA levels and triglyceride content and acetyl-CoA carboxylase mRNA levels in human liver biopsies.[28,29]

2.2. Olive Oil

The health benefits of olive oil, a key component of Mediterranean diet (MedDiet), are well known and reported in the literature.[37] Olive oil may offer health benefits as it is high in healthy monosaturated fats and antioxidants as well as for having anti-inflammatory properties.[38] The Pizarra study,[39] that evaluated more than 900 people after 6 years of consuming olive oil, found that SHBG serum levels were significantly higher in subjects using olive oil for cooking compared with subjects using sunflower oil. Remarkably, SHBG levels correlated positively with monounsaturated fatty acids (MUFAs) and negatively with saturated fatty acids. In addition, multiple regression analysis showed that MUFAs were independently associated with SHBG levels.[40] This study was complemented by in vitro experiments using HepG2 cells showing that oleoyl-CoA treatment was able to increase SHBG production by downregulating PPARγ protein levels, an inhibitor of *SHBG* gene expression.[2,29]

2.3. Red Wine (Resveratrol)

Epidemiological studies have shown that moderate red wine consumption reduces the risk of suffering cardiovascular disease (CVD).[41–44] This beneficial cardiovascular effect has been attributed to components other than alcohol,[45–47] these components are referred to as congeners of alcoholic beverages and these congeners include several polyphenols.[48] Among these polyphenols, resveratrol (3,4′,5-trihydroxystilbene), which has a potent antioxidant activity, is considered to be protective against CVD and cancer, among other diseases.[45,47–52] In a series of comprehensive experiments, we have shown that red wine and resveratrol increase SHBG production in HepG2 cells.[3] Mechanistically, resveratrol acts specifically through the human constitutive androstane receptor (CAR), a drug/xenobiotic detoxification gene regulator,[53–56] to increase hepatic SHBG production by binding to a DR-1 element, present in the footprint 3 region of the *SHBG* promoter.[3] These results were corroborated in vivo using a humanized *SHBG/CAR* transgenic mouse, where plasma SHBG levels were increased by resveratrol consumption.[3] Moreover, SHBG expression correlated significantly with CAR mRNA levels in human liver biopsies.[3] Finally, a pilot study aimed to test the effect of drinking two types of red wine with different resveratrol content was conducted in 26 healthy volunteers. The results showed that consumption of both wines did not change body mass index or biochemical markers of liver injury. However, while the low resveratrol wine did not modify the lipid profile or SHBG levels, the red wine with high resveratrol content significantly reduced total cholesterol in both men and women and increased plasma SHBG levels in women, but not in men.[57] It is also important to mention that these results agree with the results reported by Chow et al. showing an increase of 10% in plasma SHBG levels after a resveratrol treatment of 1 g daily for 12 weeks in postmenopausal women.[58]

2.4. Caffeine

A positive relationship between coffee and caffeine consumption and SHBG plasma levels has been shown in epidemiological studies.[59,60] However, the relationship between caffeine and SHBG production has never been studied before at the molecular level. Our results using HepG2 cells showed that caffeine did not increase SHBG production in in vitro experiments. By contrast, plasma SHBG levels increased in human *SHBG* transgenic mice after 12 days of drinking water supplemented with caffeine.[61] These results confirmed that caffeine increases plasma SHBG levels in vivo and strongly suggests that the underlying molecular mechanisms by which caffeine increases SHBG production is unrelated to its hepatic effects. In this regard, it is known that caffeine intake has effects on different body tissues, including adipose tissue.[62] White adipose tissue is an endocrine organ producing several cytokines, for instance adiponectin,[63] which have been already shown to increase hepatic SHBG production.[64] Since caffeine consumption is associated with higher adiponectin plasma levels in humans,[65] we decided to measure adiponectin levels in our humanized *SHBG* transgenic mice drinking caffeine supplemented water. The results showed a significant increase in plasma adiponectin levels in mice consuming caffeine in the drinking water. In addition, caffeine treated mice had higher adiponectin mRNA levels than vehicle treated mice in white adipose tissue. The later was corroborated by treating with caffeine mature 3T3-L1 mouse adipocytes, the results showed that caffeine increased adiponectin production in adipocytes through protein kinase B (AKT) signaling pathway by increasing the forkhead box protein O1 (FOXO1) protein levels,[61] a well-known transcription factor activator of adiponectin gene expression.[66]

3. Clinical Implications and Future Perspectives

One of the most important lessons of recent years has been that apart from a carrier of sex hormones, SHBG is a reliable biomarker of metabolic dysfunctions in which insulin resistance plays an essential role such as metabolic syndrome, obesity, fatty liver disease, type 2 diabetes (T2D), gestational diabetes, and polycystic ovary syndrome.[6–8,67] In addition, low plasma SHBG concentrations in overweight individuals are predictive T2D and cardiovascular disease (CVD) risk.[10–14,67] Although the potential role of SHBG per se in the pathogenesis of the above-mentioned diseases remains to be elucidated, several reports have suggested its contribution to the development and progression of obesity.[68]

The new insights from SHBG research related to nutrition reported in recent years, are based on fact that a single dietary component can potentially regulate plasmatic SHBG levels in humans. Consumption of added sugars has been related to an increased risk of several chronic diseases, including obesity, CVD, T2D, nonalcoholic fatty liver disease (NAFLD), cognitive decline, and even some cancers.[69–71] The fact that monosaccharides reduced human *SHBG* gene expression by altering hepatic HNF-4α levels provide a molecular mechanism explaining the link between the low plasma SHBG levels and the metabolic extremes in people suffering from obesity and anorexia. Interestingly, monosaccharides induced hepatic de novo lipogenesis which increased the hepatocyte palmitate content reducing HNF-4α protein levels.[28] This is important since, among the monosaccharides, fructose is the most potent inducer of de novo lipogenesis[28] and therefore explains why the *SHBG* gene expression is remarkably responsive to fructose consump-

tion. Studies in different human cohorts have shown that elevated liver fat content strongly correlated with circulating SHBG in humans.[35,36] These findings suggest that plasma SHBG levels may represent a useful biomarker of metabolic disturbances associated with excess sugar consumption.

MedDiet is a well-known and characterized diet distinguished by high intakes of vegetables, legumes, fruits, nuts, grains, fish, protein sources from seafood and poultry, olive oil and low-to-moderate intake of red wine, as well as low intake of dairy products, red and processed meat, cream, and sugar drinks.[72,73] The MedDiet is the most studied diet in the world and it has been associated with important health benefits. In this regard, several studies provided strong evidences of the MedDiet benefits on cardiovascular health, which not only includes reduction in the cardiovascular incident outcomes, but also in the associated risk factors such as obesity, hypertension, metabolic syndrome, and dyslipidemia. The MedDiet has been also related with a reduction of the risk in the development of developing T2D, a reduction in mortality and therefore an increase in longevity.[73,74] It is remarkable that olive oil and red wine, two of the most important components of MedDiet increased plasma SHBG levels, thus linking epidemiologically studies showing that subjects with low plasma SHBG levels have higher risk of suffering both CVD and T2D.[75,76] Therefore, specific studies addressed to examine the role of SHBG as an independent mediator of the relationship between olive oil and red wine consumption and the cardiovascular protective effects of the Mediterranean diet seem warranted.

Coffee is one of the most popular beverages in the world; although its impact on health outcomes and adverse effects is not fully understood. It is widely accepted that coffee consumption contributes to the prevention of inflammatory and oxidative stress-related diseases, such as obesity, metabolic syndrome, and T2D.[77] Recent results showed that caffeine upregulates hepatic SHBG expression by increasing adiponectin production through AKT/FOXO1 pathway in the adipose tissue.[61] Therefore, this could be one of the key mechanisms involved in the beneficial effects of caffeine in the prevention of metabolic diseases.

Overall, all these findings point to SHBG not only as a sex steroid carrier but also as a useful biomarker of type of diet consumption and metabolic diseases. Future research is needed in order to determine whether SHBG plasma levels could be a reliable biomarker of the success of dietary interventions in patients suffering from metabolic diseases.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Keywords

caffeine, carbohydrates, diet, human disease, Mediterranean diet, olive oil, red wine, sex hormone-binding globulin

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Laura Brianso-Llort did her PhD working in SHBG regulation and role in human disease development under the supervision of Dr. Selva DM at the Diabetes and Metabolism Department of the Vall d'Hebron Research Institute (VHIR).

Cristina Saéz-Lopez did her PhD working in SHBG regulation and role in human disease development under the supervision of Dr. Selva DM at the Diabetes and Metabolism Department of the Vall d'Hebron Research Institute (VHIR).

Anna Alvarez-Guaita did her PhD working in liver physiology and regeneration in the University of Barcelona and IDIBAPS (Institut d'Investigacions Biomédiques August Pi i Sunyer). Then, she moved to Cambridge asa postdoctoral fellow to work with Prof David B Savage and Sir Stephen O'Rahilly in the Institute of Metabolic Sciences-Metabolic Research Laboratories (MRL-IMS) at the University of Cambridge. In 2022, Dr. Anna Alvarez-Guaita joined Dr. Selva DM research group at the Diabetes and Metabolism Department of the Vall d'Hebron Research Institute (VHIR).

Lorena Ramos has more 15 years of experience working as a laboratory technician and laboratory manager at the Diabetes and Metabolism Department of the Vall d'Hebron Research Institute (VHIR).

Cristina Hernandez is responsible for the lines of research in non-classical cardiovascular risk factors and diabetic retinopathy of the Diabetes and Metabolism Research Group of the Vall d'Hebron Hospital Research Institute (VHIR) and Head of Section of the Health Service Endocrinology and Nutrition at the Vall d'Hebron Hospital. She is the author of more than 300 articles (H Index: 59. Citations: 12,574) and has participated in 45 research projects related to diabetes (12 as PI). It is worth mentioning that he has been Scientific Manager of the European consortium EUROCONDOR (European Consortium for the Early Treatment of Diabetic Retinopathy).

Rafael Simó is the Chair of the Division of Endocrinology and Nutrition at Vall d'Hebron University Hospital, Director of Diabetes and Metabolism Research Unit at Vall d'Hebron Research Institute (VHIR), Professor of Medicine & Endocrinology at the Autonomous University of Barcelona, Deputy Director of Clinical Research at VHIR. Prof. Simó (Hirsch index: 68) has authored over 450 articles related to diabetes, besides 14 book chapters. He has participated in 28 research projects related to diabetic retinopathy and in 34 projects related to clinical diabetes. He has been the Coordinator of 2 European projects (EUOCONDOR and RECOGNISED).

David M. Selva is a Senior Researcher and Group Leader of the SHBG in human disease group at the Diabetes and Metabolism Department at Vall d'Hebron Research Institute (VHIR). Associate Professor at the Autonomous University of Barcelona (UAB). Dr Selva DM (h-index 29 and i10-index 35) has authored more than 40 articles and he has participated in more than 10 research projects. The results of his research have generated several patents and he has created two spin-off companies.