

Study on the Relationship of 25-hydroxyvitamin D and Intact Parathyroid Hormone in Chinese Young Adults

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Research

Keywords: 25-hydroxyvitamin D, parathyroid hormone, plateau, Chinese young adults

Posted Date: March 23rd, 2020

DOI: <https://doi.org/10.21203/rs.2.21603/v2>

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Abstract

Background : Vitamin D plays an important role in bone health and other diseases, however, there is no consensus over the optimal serum 25-hydroxyvitamin D (25(OH)D) concentration. Many studies defined a level of serum 25(OH)D at which serum intact parathyroid hormone (iPTH) levels decreased and reached a plateau might be the optimal status for vitamin D sufficiency. This study was performed to study the relationship between 25(OH)D concentration and intact parathyroid hormone (iPTH) concentration in the Chinese non-clinical young population aged 18-44y.

Methods : The serum samples of young adults aged 18-44 years old were selected from the established serum bank of Chinese Chronic Diseases and Nutrition Survey (CCDNS, 2015-2018). The serum 25(OH)D concentration was determined by high performance liquid chromatography tandem mass spectrometer, and the iPTH was determined by electronic chemiluminescence method. The relationship of 25(OH)D and iPTH were analyzed by partial correlation analysis, and the threshold of 25(OH)D was analyzed by locally weighted scatter plot smoothing method after adjusting the iPTH by age, season of blood draw, BMI, waist, sex and latitude.

Results : 623 serum samples (293 male, 330 female) of 25(OH)D concentration and iPTH concentration were analyzed. Significant higher 25(OH)D concentration was found in male than female. And the samples from the southern China had higher 25(OH)D concentration than those from the northern China. Samples from autumn had higher 25(OH)D concentration than those from spring and winter. The inversely relationship between 25(OH)D concentration and iPTH concentration was observed when the 25(OH)D was below 17.6 ng/mL for both sexes. The threshold for male was 16.2 ng/mL and it was 25.6 ng/mL for female.

Conclusions : The threshold and the relationship between 25(OH)D and iPTH differs by sex among Chinese young adults aged 18-44y. Further study is needed to evaluate the sex-specific ranges of optimal vitamin D.

Trial registration : Not applicable.

Background

Vitamin D is one of the essential micronutrients in human body. Vitamin D can stimulate the synthesis of osteopontin and alkaline phosphatase in osteoblasts and inhibit the apoptosis of osteoblasts, which is beneficial to bone formation [1]. Recent studies have found that vitamin D nutritional status is not only related to bone health, but also to cell metabolism, immune system, respiratory system and other human functions [2,3]. On the other hand, vitamin D excess can lead to hypocalcaemia [4], therefore it is very important to accurately evaluate the nutritional status of human vitamin D for early prevention and treatment of related diseases.

25-hydroxyvitamin D [25(OH)D] is the main circulation form of vitamin D in blood with a half-life of 2-3 weeks [5]. It is recognized as a reliable indicator for evaluating vitamin D status in human body [6]. However, there are still controversies about the threshold of 25(OH)D in serum for judging the nutritional status of vitamin D. There are two main popular perspectives of thresholds for vitamin D deficiency recommended by the American Institute of Medicine (IOM) and the Endocrine Society (TES), respectively [5,7]. The Institute of Medicine (IOM) of America considered that a serum 25(OH)D level of at least 20 ng/mL (50 nmol/L), meet the requirements of at least 97.5% of the population. And it defined vitamin D deficiency as <12 ng/ml (30 nmol/L) 25(OH)D and considered levels between 12-20 ng/ml (30-50 nmol/L) as insufficient vitamin D [6,8]. TES issued serum 25(OH)D level of 30 ng/mL (75 nmol/L) was considered sufficient. Serum 25(OH)D level that was lower than 20 ng/mL (50 nmol/L) as vitamin D deficiency and serum 25(OH)D level between 20-30 ng/mL (50-75nmol/L) as vitamin D insufficiency [5].

Intact Parathyroid hormone (iPTH) is a calcium-regulated hormone and it mainly acts on kidney and bone tissues. iPTH concentration has been reported inversely associated with serum 25(OH)D concentrations until a threshold, and then the iPTH concentration reaches its plateau at a minimum level above the threshold[9]. This threshold and above is often suggested as Vitamin D sufficiency [10-11]. There are a number of cross-sectional and randomized controlled trials report on the inversely relationship between 25(OH)D concentration and iPTH concentration in different countries and ethnicities [10-11]. There was no consistency in the threshold values of serum 25(OH)D that varies from 25 nmol/L (10 ng/mL) to 50 nmol/L (125 ng/mL) [10]. There are still some studies in which such threshold or the negative correlation was not found.

This study is to analyze the relationship between serum 25(OH)D concentration and iPTH concentration in Chinese young adults aged 18-44y based on the Chinese Chronic Diseases and Nutrition Survey (CCDNS) 2015-2018. We try to understand if there is such a threshold for this specific group of Chinese population.

Methods

Study population

650 samples of adults aged 18-44y were collected from the Chinese population serum bank established from the CCDNS 2015-2018 by the method of simple random sampling. CCDNS is a cross-sectional survey of the civilian non-institutionalized population of China, conducted by the National Institute of Nutrition and Health and the Center for the Prevention and Control of Chronic Non-communicable Diseases, Chinese Center for Disease Control and Prevention (NINH & CPC, China CDC). All the participants of this survey were selected by using a stratified proportional random cluster sampling. All the participants and their guardians gave their informed consent in writing to participate in the CCDNS survey.

25(OH)D and iPTH detection

Both serum 25(OH)D and serum iPTH were detected in this study. 2 mL of fasting venous blood was collected and centrifuged at 1500× g for 15 min, 20-30 min after the blood was taken. The serum was aliquot and stored in a brown vessel at -20°C in the laboratory where the investigation area was located. All the serum specimens from all the investigation areas were transported to the serum bank located in NINH by cold chain. All the blood samples were preserved at -70°C in a freezer before detection. The High Performance Liquid Chromatography Tandem Mass Spectrometer (AB Sciex Pte. Ltd. USA) was used to analyze serum 25(OH)D concentration. The calibration of the assay was verified by using the NIST standard reference material SRM 972. The average bias was 2.3% for 25(OH)D₂ and 1.7% for 25(OH)D₃ comparing with Nist SRM 972. The iPTH concentration was measured by electronic chemiluminescence immunoassay (Roche e601, F Hoffmann-La Roche Ltd. Switzerland). The CV was 4.9% in the 51.5-53.9 pg/mL range, and 4.2% in the 186-191 pg/ml range.

Variables

A national project workgroup was established in China CDC to develop a unified survey and questionnaires to carry out the investigation by using unified equipments and methods. The basic information of the subjects (including age, sex, region type, etc.) was collected by questionnaire. China's Qinling Mountains and Huaihe River are recognized as the boundary to divide the north and the south. The latitude of each investigation area was searched from Google map. The region type are classified according to the level and type of economic development and the population size [12]. Body Mass Index (BMI) was calculated according to bodyweight and height. Waist was measured by the uniformed method. Body weight was measured by uniform electronic scale, and standing height was measured by a metal column type height meter.

Statistical Analysis. Serum 25(OH)D and iPTH concentrations were recorded by using P50 (P25–P75) because they were not compliant with the normal distribution according to the normality test, and then they were compared by the Kruskal–Wallis test in different subgroups. The correlation was analyzed by spearman correlation method among 25(OH)D, iPTH, season, age, sex, latitude, bmi, waist. Adjusted by age, BMI, latitude, waist and season, the correlation between the 25(OH)D concentration and the iPTH concentration was analyzed by the partial correlation analysis. The generalized additive model was adopted and applied by mgcv package in R software to generate an adjusted iPTH to adjust the potential factor that may have influence on iPTH, 25(OH)D or both of them, such as BMI, age, latitude, waist, season of blood draw, sex. The adjusted iPTH for each sex were also made. And the adjusted iPTH concentrations were used for the following analysis. The locally weighted scatterplot smoothing (LOESS) procedure is a nonparametric method for fitting a smooth curve that best characterizes the relationship between 2 continuous variables [13]. Given the reported non-linear association between iPTH and 25(OH)D, the LOESS curve was then utilized to characterize the association between them, and then the threshold was predicted. The SAS version 9.4 statistical software (SAS Institute Inc., Cary, NC, USA) and R version 3.6.1 statistical software were used. Two tailed $P < 0.05$ was considered as statistically significant.

Results

Sample characteristics

Samples of poor blood quality or those with incomplete information were excluded, and the serum 25(OH)D concentration and iPTH concentration of 623 blood samples (293 male and 330 female) aged 18-44y were included in this study (Table 1). The samples were collected from all 31 provincial administrative regions in China. The male samples covered 209 survey areas, and the female samples covered 196 survey areas. The median age was 31(25-39) years old. The median BMI was 23.1(20.9-25.6) kg/m², and female had a statistically lower BMI than male (P=0.009). The median waist was 86.9(72.5-86.9) cm, and male was significantly higher than that of female. The median iPTH concentration was 24.2(18.1-31.7) pg/mL with the range of 5.5-96.4 pg/mL, and no statistical difference was found between male and female in all age groups. No statistical difference was found in all age groups in terms of iPTH and 25(OH)D concentration in both sex. The distribution of iPTH by sex was showed in Figure 1. The median 25(OH)D concentration was 19.1(13.2-26.1) ng/mL with the range of 3.2-57.8 ng/mL. Male had a significant higher 25(OH)D concentration than that of female in all age groups and both region types. The distribution of 25(OH)D by sex was showed in Figure 2. The 25(OH)D concentration of the serum samples from the north was significantly lower than those from the south in both sexes. No statistical difference was found in different region types in both sexes. As CCDNS did not conduct the investigation on a seasonal basis, our samples did not cover all the seasons; summer was not included. In this study, the median 25(OH)D level was highest in autumn. No significant difference was found in spring, autumn and winter in terms of the median iPTH concentration.

Table 1 25 hydroxyvitamin D and intact parathyroid hormone concentration of Chinese adults aged 18-44y.

Characteristic	Total	Male	Female	<i>P</i> ^a
Sample size(n,%)	623	293(47%)	330(53%)	
Age(y)	31(25-39)	30(24-38)	31(25-39)	0.37
BMI(kg/m ²)	23.1(20.9-25.6)	23.7(21.4-26.3)	22.8(20.7-25.0)	0.009
Waist (cm)	86.9(72.5-86.9)	83.9(75.6-90.1)	76.4(71.0-83.7)	<0.001
iPTH(pg/mL)	24.2(18.1-31.7)	24.0(18.0-30.2)	24.3(18.2-32.4)	0.30
Age group (iPTH, pg/mL)				
18-25y	23.7(18.6-29.9)	23.9(17.8-29.3)	23.6(18.8-31.8)	0.46
26-35y	24.2(17.2-31.6)	23.9(17.7-30.4)	24.3(17.1-32.1)	0.82
36-44y	24.8(18.8-32.3)	24.1(18.2-31.6)	25.1(19.8-33.6)	0.42
Latitude (iPTH, pg/mL)				
North	24.9(18.2-32.3)	23.7(17.8-31.1)	25.2(18.7-33.5)	0.09
South	23.8(17.8-30.4)	24.2(18.2-29.9)	23.1(17.6-31.5)	0.76
Region type (iPTH, pg/mL)				
Urban	25.0(19.1-31.8)	24.9(19.5-31.6) ^d	23.4 (17.1-29.0)	0.83
Rural areas	23.8(17.5-31.0)	25.2(19.1-31.9)	24.7(17.7-33.6)	0.74
Season (iPTH, pg/mL)				
Spring	25.3(19.0-31.8)	24.8(17.7-31.8)	25.7(19.5-31.7)	0.88
Autumn	23.9(18.2-30.4)	23.8(18.3-29.9)	23.9(17.8-31.5)	0.97
Winter	24.4(17.8-32.5)	24.0(17.5-31.2)	25.0(18.1-33.5)	0.17
25(OH)D(ng/mL) ^b	19.0(13.2-26.1)	20.9(15.4-28.2)	17.2(12.2-23.6)	<0.001
Age group (25(OH)D, ng/mL)				
18-25y	18.1(12.2-24.9)	19.4(14.0-27.7)	16.6(11.7-22.6)	0.02
26-35y	18.3(13.3-26.1)	20.5(15.1-27.8)	17.1(12.5-24.2)	0.007
36-44y	20.7(14.5-28.0)	21.9(16.6-30.2)	18.2(12.8-25.6)	0.001
Latitude (25(OH)D, ng/mL)				
North	14.4(10.6-20.4) ^c	17.6(11.9-23.5) ^c	12.7(10.1-17.4) ^c	<0.001
South	23.6(17.4-29.9)	25.0(18.4-32.9)	22.4(17.1-28.3)	0.01
Region type (25(OH)D, ng/mL)				
Urban	18.3(12.5-24.9)	20.5(14.2-27.1)	16.2(11.7-22.7)	0.004
Rural areas	19.2(13.7-26.8)	21.2(15.8-29.0)	17.4(12.8-25.2)	<0.001
Seasons (25(OH)D, ng/mL)				
Spring	17.4(11.8-26.1)	18.4(11.8-27.1)	15.9(11.8-21.6)	0.36
Autumn	20.9(15.2-28.3) ^e	22.3(15.9-30.4) ^e	19.9(14.4-26.2) ^e	0.01
Winter	17.2(11.9-23.8)	19.4(14.3-25.7)	15.0(10.7-21.5)	<0.001

¹ Age, BMI, 25(OH)D concentration and iPTH concentration were all recorded by using P50 (P25–P75) due to not compliant with normal distribution. ^a Difference between sexes; ^b To convert to nmol/L, multiply ng/mL by 2.5; ^c Significant different from the south, *P*<0.05; ^d Significant different from the rural areas, *P*<0.05; ^e Significant different from the other seasons, *P*<0.05.

Serum 25(OH)D and its correlation with iPTH

The correlation results showed that 25(OH)D was correlated with iPTH, latitude, sex, season and age, and iPTH was correlated with BMI and waist ($P < 0.05$) (Supplemental Table S1). The 25(OH)D concentration was correlated with iPTH, age, latitude and waist in males, while it was correlated with iPTH, season and latitude in females. The iPTH was correlated with BMI and waist in males, and it was correlated with waist in female (Supplemental Table S2-S3). The results of age, BMI, latitude, waist and season adjusted partial correlation analysis showed that the serum 25(OH)D was inversely associated with the serum iPTH concentration in both sexes (male, $r_s = -0.20$, $P = 0.0008$; female, $r_s = -0.20$, $P = 0.0009$).

The scatter plot of iPTH concentration by 25(OH)D concentration and corresponding LOESS curve was showed in Figure 3. The inversely correlation between iPTH concentration and 25(OH)D concentration was apparent according to the scatter plot. The inversely relationship was observed between PTH and 25(OH)D when 25(OH)D concentration was below 17.6 ng/mL after adjusted by covariates (Supplemental Figure S1). As for male, the threshold was 16.2 ng/mL and it was 25.6 ng/mL for female.

Discussion

As early as 1987, researchers began to study the relationship between vitamin D and iPTH by cross-sectional studies or randomized controlled trials to search the plateau period of iPTH and the corresponding 25(OH)D concentration among different groups, including the elderly, female, healthy adults, vitamin D-deficient people, etc [14-15]. Survey data from NHANES 2003-2004 and 2004-2005 shows that the relationships among 25(OH)D, BMD and PTH in American adults vary according to race/ethnicity. Significant inverse relationship between 25(OH)D and iPTH values was only observed when 25(OH)D concentrations were below 26 ng/ml among blacks, while inverse relationship was observed above and below a 25(OH)D level of 20 ng/ml in whites and Mexican-Americans [14]. Aloia et al. [16] found that iPTH reached plateau stage when the serum 25(OH)D concentration was between 40-50 nmol/L (16-20 ng/mL) of African American women. In addition to the above studies, there are also studies that failed to find the threshold [10, 17]. Different races and genetic backgrounds might explain the phenomenon, and it is necessary to study whether the same cutoffs are suitable for different ethnicity.

This is the first national cross-sectional study on the threshold of 25(OH)D among Chinese population. In our study, we analyzed the threshold when iPTH reaching plateau stage by sex, because of the significant difference in the distribution of 25(OH)D levels between male and female. We found that the concentration of 25(OH)D was 19.2 ng/mL (48 nmol/L) while not adjusted by covariates when iPTH entered into its plateau in Chinese women aged 18-44y. It is close to the threshold of 50.8 nmol/L (20.3 ng/mL) in adult of both sex aged 20-45y in Shanghai city, China reported by Yao et al [18]. The threshold for 25(OH)D was 17.6 ng/mL after adjusted by sex, age, latitude, BMI, waist and season of blood draw. It was close to IOM' recommendation and similar with most study reported [10]. The threshold of male (16.2 ng/mL) was obviously lower than that of female (25.6 ng/mL). Both of the thresholds were within the most frequent range of literature reports. There are few studies about the threshold of male reported, scattered in the range of 15-20ng/mL, followed by 30-35ng/mL [10]. The threshold for the deficiency of sex could be better explored and analyzed with more relevant indicators, such as calcium and vitamin D intake, renal function, bone health indicators, endocrine indicators, etc. Arabi et al. [19] think that age but not gender modulate the relationship between 25(OHD) and PTH among adolescents (10-17 years) and elderly (65-85 years) of the same ethnic group living in Lebanon. No age specific difference was found in terms of relationship between 25(OH)D and iPTH in this study, probably because of the concentrated age distribution. However, the sex differences of threshold was found in the relationship of 25(OH)D and PTH in our study. Similar sex differences were reported by a cross-sectional study conducted among adolescents aged 12-15y in North Ireland, where the researchers found a threshold at 60 nmol/L (24 ng/mL) in girls, however, no cutoff was found in boy [20]. Although 25(OH)D level of male was significantly higher than that of female, iPTH did not differ significantly. This might also indicate that the corresponding iPTH was no longer decreased when the level of 25(OH)D increases to a certain range. The secretion of sex hormones and growth hormone might also be associated with the sex difference. The results from different studies is controversial regarding the relationships of 25(OH)D concentration with levels of sex hormones and gonadotropins [21]. Frank et al consider that the impact of sex hormone on skeletal metabolism was different between sexes [22, 23]. Besides the intake of vitamin D and calcium, the nutritional status, such as vitamin K nutritional status which has synergetic effect with vitamin D, extent of outdoor activities might be others reason for the disparity between sexes in terms of 25(OH)D. Further study should also be made to reveal the difference between sexes. We also found the disparity of 25(OH)D concentration in different seasons. Though no samples for summer in our study, the seasonal distribution of 25(OH)D concentration is consistent with our former study [24] and the report from Kroll et al. in the United States [25]. In their study, they found the lowest concentration of iPTH occurs 3.5 weeks after the 25(OH)D₃ reaches its highest concentration and vice versa. We can hardly tell the impact of relationship between iPTH concentration and 25(OH)D concentration, because our samples are limited and not distributed to every month of a year. Further study should also be made to explore the impact of seasonal factor on the relationship between iPTH and 25(OH)D.

The vitamin D insufficiency and deficiency of Chinese adults aged 18-44y was 34.5% and 19.4%, respectively, according to IOM's recommendation. The vitamin D insufficiency and deficiency reached to 30.7% and 53.9%, respectively, and only 15.4% was sufficient when adopting TES's recommendation. The

median 25(OH)D concentration was 19.1(13.2-26.1) ng/mL, and it is apparently lower than 10 years ago [26]. Less outdoor time, the use of sunscreen might partly explain the reduction of 25(OH)D concentration. Higher 25(OH)D concentration in southern area attributes to stronger ultraviolet radiation in southern area than in the northern area. We suggest exploring sex specific thresholds by taking into consideration potential impact of physiological differences between male and female. Although there are significant differences in 25(OH)D levels between the northern and southern populations in Chinese adults, it is difficult to distinguish individuals strictly according to regions due to population mobility, topographic differences, and etc. For these reasons, we do not recommend setting different boundaries for different regions.

We acknowledge several limitations. First, the limited samples size. Although samples in this study covered all the provincial administrative regions in China, the sample size was only up to 623 cases. In particular, there were only 10 samples in April, which may also lead to the deviation of results. Since this study is an exploratory study in this field of China, the sample size was small indeed, and we will increase the sample size in subsequent studies. Secondly, the dietary sources of vitamin D and calcium intake [26], bone health indicators, inflammatory factors, and other factors that may influence the relationship between iPTH and 25(OH)D, were not included in this study. Due to the above factors, it may lead to bias in the relationship or threshold between iPTH and 25(OH)D in this study.

Conclusions

In summary, although the present study was hindered by some limitations, we still find a threshold for Chinese adult aged 18-44y at 17.6 ng/mL for both sexes (16.2 ng/mL for male and 25.6 ng/mL for female, respectively), above which we consider the vitamin D status is sufficient. The relationship between 25(OH)D and iPTH differs by sex, and further study is needed to evaluate the sex-specific ranges of optimal vitamin D by increasing sample size and adding more related indicators.

Abbreviations

25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; CCDNS, Chinese Chronic Diseases and Nutrition Survey; NINH, National Institute of Nutrition and Health; CPC, the Center for the Prevention and Control of Chronic Non-communicable Diseases; China CDC, Chinese Center for Disease Control and Prevention; BMI, Body Mass Index; LOESS, locally weighted regression smooth scatterplot;

Declarations

Ethics approval and consent to participate

The data of this study was from the Chinese Chronic Diseases and Nutrition Survey 2015-2018. The CNNHS 2015-2018 was given ethical approval by Ethics Review Board of Chinese Center for Disease Control and Prevention (No. 201519-A).

Consent for publication

The data of this study did not include personal information (i.e., name or address). All participants were adults.

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research was funded by the Chinese National Natural Science Foundation Project: Study on defining physiologically "normal" vitamin D in apparent healthy Chinese childbearing women (No. 81872627).

Author's Contributions

All authors have read and agree to the published version of the manuscript. Conceptualization, Yichun Hu and Lichen Yang; Data curation, Yichun Hu; Investigation, Yichun Hu and Siran Li; Methodology, Yichun Hu and Lichen Yang; Software, Yichun Hu; Supervision, Lichen Yang and Xiaoguang Yang; Validation, Yichun Hu and Zhen Liu; Writing – original draft, Yichun Hu; Writing – review & editing, Yichun Hu, Lichen Yang and Xiaoguang Yang.

Acknowledgments

We thank all the participants in our study and all the staff working for the Chinese Chronic Diseases and Nutrition Survey (CCDNS 2015-2018). We thank Dr. Tianjin Chen for language improvement and Zhijun Chen for statistical analysis.

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Figures

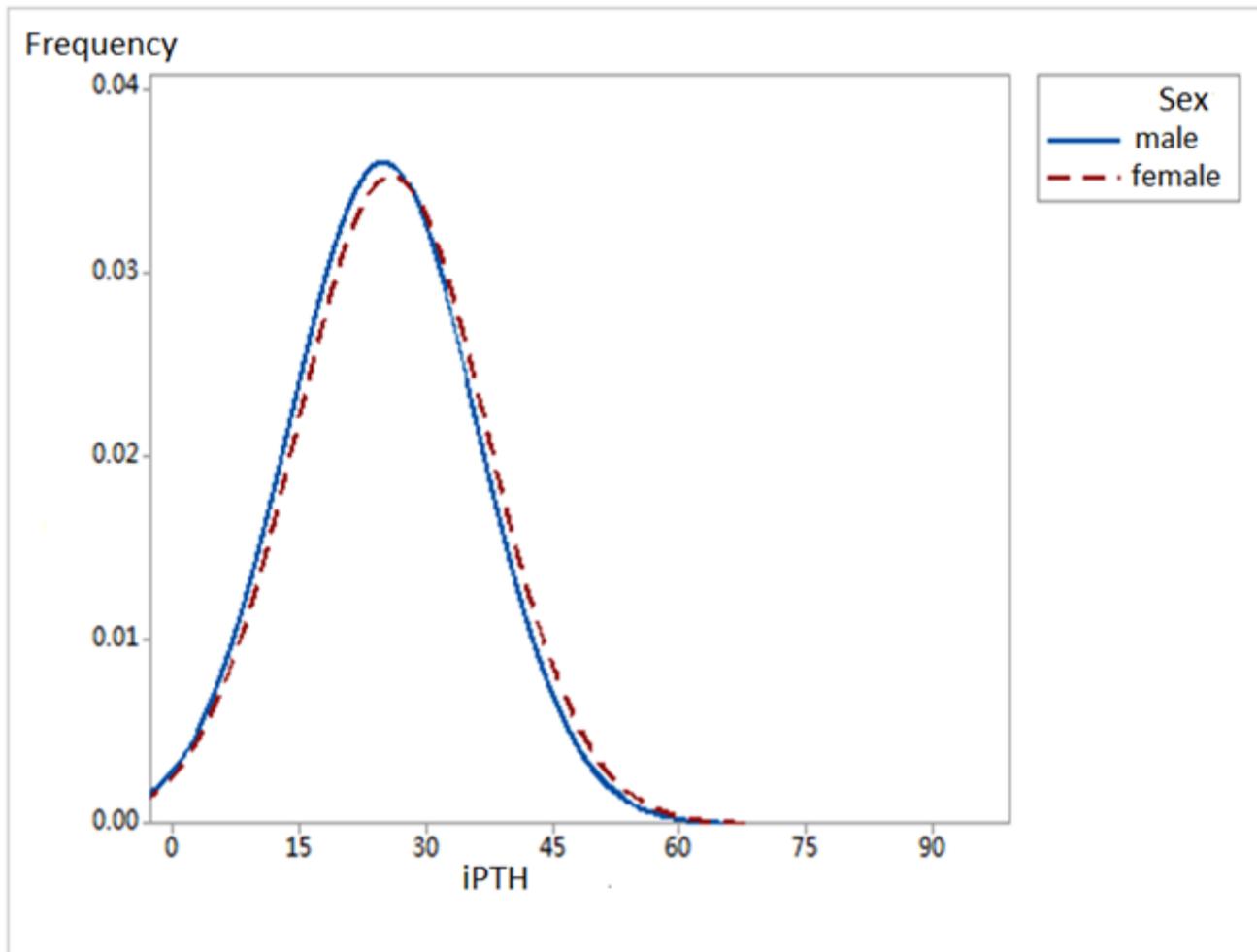


Figure 1

Distribution of intact parathyroid hormone (iPTH) by sex

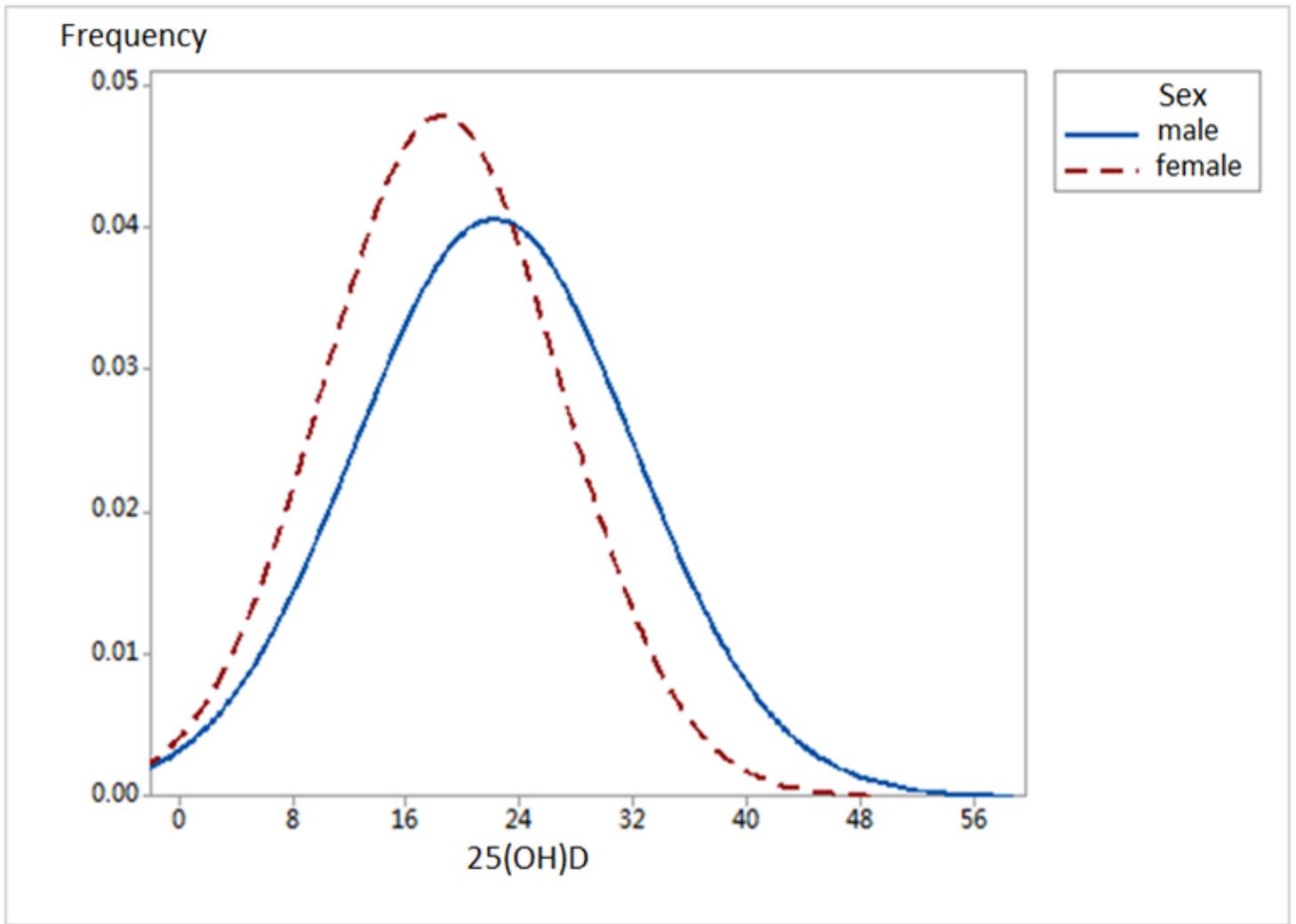


Figure 2

Distribution of 25 hydrovitamin D by sex

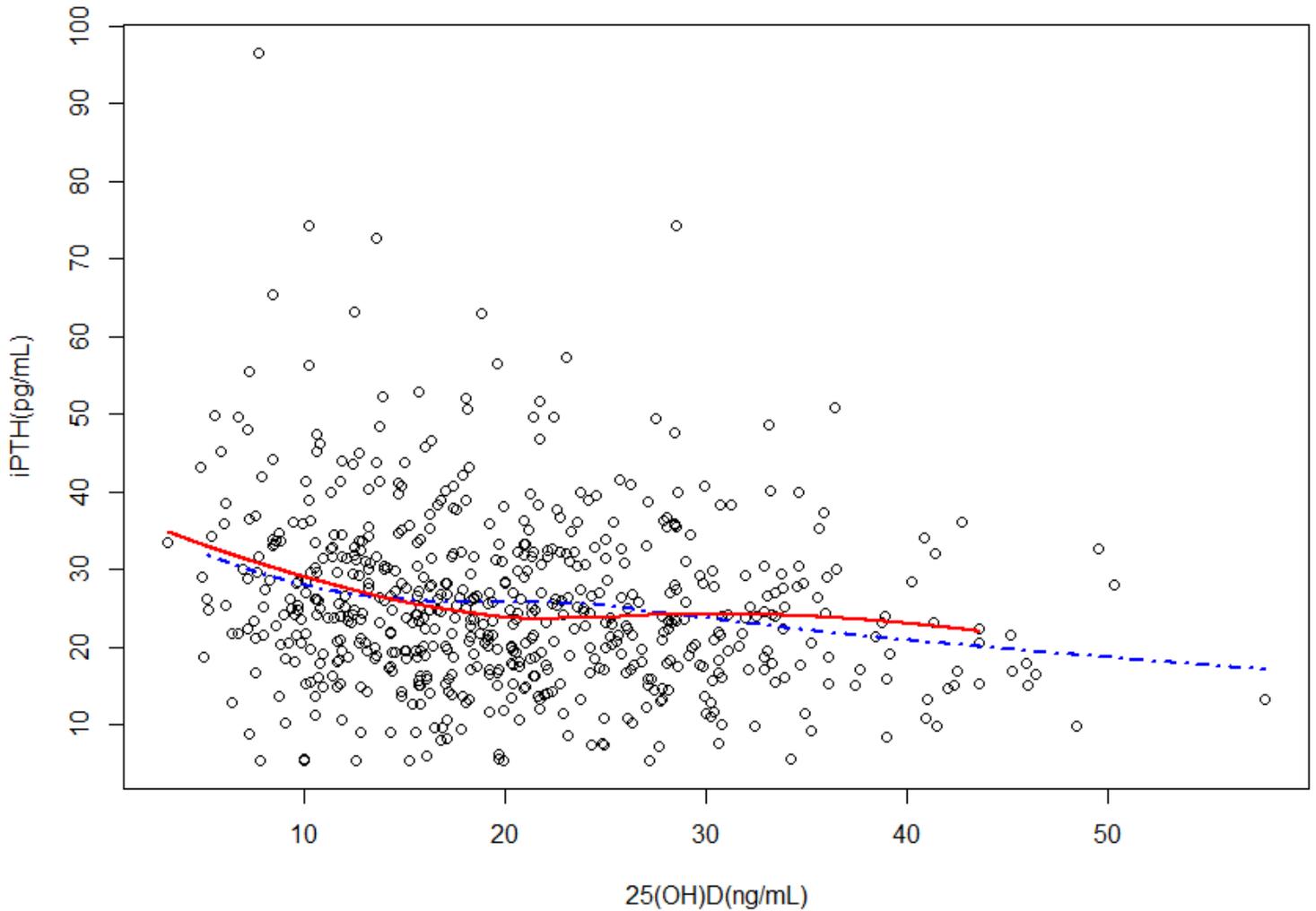


Figure 3

The Relationship between 25(OH)D and intact parathyroid hormone (iPTH) by sex – LOESS Plot (male, blue and dotted line; female, red and solid line).

Supplementary Files

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