Optimization of Epicardial Fat Thickness Change in Obese Patients with Weight Loss by Bariatric Surgery Using Central Composite and Box-Behnken Design

Ferhan Elmalı
Izmir Katip Celebi Universitesi Tip Fakultesi
Mustafa Agah Tekindal (matekindal@gmail.com)
Izmir Katip Celebi Universitesi Tip Fakultesi https://orcid.org/0000-0002-4060-7048
Cihan Altın
Baskent Universitesi Tip Fakultesi
Can Ateş
Aksaray Universitesi
Varlık Erol
Baskent Universitesi Tip Fakultesi

Research

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Posted Date: July 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-39583/v1

Optimization of Epicardial Fat Thickness Change in Obese Patients with Weight Loss by Bariatric Surgery Using Central Composite and Box-Behnken Design

Ferhan Elmalı[1], **Mustafa Agâh TEKİNDAL[1]**, Cihan ALTIN[2], Can ATEŞ[3], Varlık EROL[4]

[1]İzmir Katip Çelebi Uni. Faculty of Medicine, Department of Biostatistics, İzmir, elmalıiferhan@yahoo.com, matekindal@gmail.com

[2] Başkent Uni. Faculty of Medicine Zübeyde Hanım Research and Appl. Center, Cardiology Dep., İzmir, drcihanaltin@hotmail.com

[3] Aksaray Uni. Faculty of Medicine, Department of Biostatistics and Medical Informatics, Aksaray, can.ates@gmail.com

[4] Başkent Uni. Faculty of Medicine Zübeyde Hanım Research and Appl. Center, Department of Gen. Surgery, İzmir, varlikerol@gmail.com

ABSTRACT

Background: The aim of our study was to determine the optimization of the change in epicardial fat thickness in obese patients who underwent bariatric surgery with Central Composite (CCD) and Box-Behnken Experimental design (BBD).

Methods: Response Surface Methods are used to see the sensitivity of the assessment criterion to changes in design variables, and even to obtain the necessary correlations experimentally. Response surface methods are evaluated in two different ways as CCD and BBD design. In this study, 3^3 experimental designs were designed. The study data consisted of 40 obese patients who lost weight by bariatric surgery between February 2015 and December 2016. Body Mass Index (BMI), Age and HOMA values were evaluated in 3 categories and 3 levels, and response variable was the change in Epicardial Fat Thickness (ΔEFT).

Results: As a result of CCD analysis, Age = 30.52, BMI = 45.30, HOMA = 34.62, the optimum ΔEFT = 2.571. As a result of BBD analysis, Age = 38.36, BMI = 63.18, HOMA = 14.95, the optimum ΔEFT = 3.756. Optimum ΔEFT is modeled with Contour and Response surface graphics.

Conclusion: According to the results of the analysis, it was found that BBD analysis for optimum ΔEFT was more positive than CCD and optimum age, BMI and HOMA combinations were determined to reach maximum ΔEFT.

Keywords: Response surface methodology, Central composite design, Box-Behnken design, Bariatric Surgery

1. INTRODUCTION

Although factorial trials may be applied in all areas of research, biology is particularly common in medical practice. Because biological events are under the influence of multiple factors. Therefore, we need to examine the effects together in any biological event to get closer to the reality. In factorial trials, different levels of multiple factors are studied at the same time and the status of a factor can be addressed at different levels of other factor or factors.

None of the combinations tried may be the best. In other words, the highest yielding combination can be found in or outside the trials. Therefore, a large number of factor combinations are needed in factorial trials. However, it is very expensive to do such trials and in addition, as the number of factors increases, it is difficult to find the homogeneous test material necessary to test all combinations. Therefore, to find the most appropriate combination of factors, statistical methods that do not require the conduct of trials involving all combinations have been developed. These methods basically carry out the first attempt by designing a relatively limited trial area, taking advantage of previous studies or similar trials, and combinations that only determine the points in this area. From the results of this experiment, firstly the point of the highest yielding factor levels is estimated, then the point where the actual optimum point is reached or by using the coefficients of the second degree response surface function of the first trial results (steepest ascent method). The highest optimization is attempted to be found [1].

It is well known that obesity is one of the greatest public health challenges and individuals with obesity have increased mortality related to cardiovascular disease (CVD) throughout in their life. Bariatric surgery is treatment of choice when all the other pharmacological and non-pharmacological approaches fail to provide desired results. Epicardial fat thickness (EFT) has been suggested as a new cardio-metabolic risk factor [2-3-4]. It was previously showed that increased EFT which is an predictor of visceral adiposity and early atherosclerotic structural changes may be reversed by sustained weight loss following bariatric surgery in asymptomatic obese patients in a prospective study design [5].

The aim of our study was to determine the optimization of the change in EFT in obese patients who underwent bariatric surgery with Central Composite (CCD) and Box-Behnken Trials (BBD).

This study was approved by Baskent University Institutional Review Board and Ethics Committee and supported by Baskent University Research Funding (Approval number: KA16/281). The study data consisted of 40 obese patients who lost weight by bariatric surgery between February 2015 and December 2016. Body Mass Index (BMI), Age and HOMA values were evaluated in 3 categories and 3 levels, and response variable was the change in Epicardial Fat Thickness (ΔEFT).

2. METHODS

A first order model should have to be a linear structure. However, the curvature test may reveal the presence of curvature. In this case, second order response surface analysis should be used.

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{12} x_1 x_2 + \varepsilon \tag{2.1}$$

This model is called the second order response surface model. This trial order has some characteristics [2,3,4].

i) Each factor must have at least 3 levels.

ii) The model shall have at least 1 + 2k + k (k-1) 2 different parameters. As a result, the trial order 1 + 2k + k (k-1) should contain data from 2 different points.

In these experiments, the point where the dependent variable takes its maximum or minimum value is called stationary point [9]. This point is located at the center of the system shown as ellipses. In some cases, the central point in the center indicates neither the maximum nor the minimum value. In this case, the static point is called the saddle point, and the system is called saddle system. One of the most important points in the method of second order response surfaces are stationary points. 3D graphics (response surface and contour graph) helps to determine these points.

2.1 Calculation of constant points

The determination of the components in the second order response surface method depends on the size of the coefficients given in the regression equation. The steps to calculate the constant points are as follows.

i) A second order response surface model is estimated by the help of the data obtained from the experiment.

ii) For each of the factors included in a model, partial derivatives are taken and equalized to zero.

$$\frac{\partial \hat{Y}}{\partial \chi_1} = \frac{\partial \hat{Y}}{\partial \chi_2} = \ldots = \frac{\partial \hat{Y}}{\partial \chi_j} = 0 \tag{2.2}$$

iii) Equivalent which obtained in step ii. (2.2) solves the equation system. A value will be obtained for each factor. These values are substituted in the model and the predicted variable value is obtained for the stationary points.

It is also possible to obtain constant points with matrices. If the given model is expressed in matrices;

$$\hat{Y} = b_1 + x'b + x'\hat{B}\chi \tag{2.3}$$

At Equation 2.3 b_1 shows the model constantb and $\hat{B}$ indicates the expected values of second order model coefficients.

$$x' = \lfloor x_1, .. x_j \rfloor \tag{2.4}$$

$\hat{B}$ is a symmetric matrix.

$$\hat{B} = \begin{bmatrix} b_{11} & \frac{1}{2}b_{12} & & \frac{1}{2}b_{1q} \\ \frac{1}{2}b_{12} & \frac{1}{2}b_{22} & & \frac{1}{2}b_{2q} \\ & & & \\ \frac{1}{2}b_{1q} & \frac{1}{2}b_{2q} & & b_{qq} \end{bmatrix} \tag{2.5}$$

Constant Points

$$x_S = \frac{1}{2}\hat{\beta}^{-1}b \tag{2.6}$$

Equation is available from 2.6. If we replace the static points in the main equation;

$$\hat{Y}_S = b_0 + x'_S\, b + x'_S\, \hat{B}x_S$$

$$\hat{Y}_S = b_0 + \frac{1}{2}x'_S\, b \tag{2.7}$$

Equation 2.7 will be obtained.

$\hat{Y}_S$ is the predicted value of the response variable from the constant point [8,10,11,12].

2.2. Structure of Constant Point (Canonical Analysis)

When a quadratic equation is found to be sufficient, Canonical analysis is applied to decide about the location and structure of stationary points. The structure of the stationary point determines the marks of the eigenvalues obtained by the matrix $\hat{\mathrm{B}}$. For this, it is possible to write a new equation containing canonical variables.

$$\hat{Y} = \hat{Y}_S + \sum_{j=1}^{k} \lambda_j W_j^2 \tag{2.8}$$

Equation 2.8 shows the eigenvalues to be derived from the $\lambda_1, \lambda_2, \ldots, \lambda_k$ $\hat{\beta}$ vector, while $\mathrm{W}_1, \mathrm{W}_2, \ldots, \mathrm{W}_k$ is called canonical variables. It is possible to understand the properties of the constant points obtained with the help of Equation 2.8.

i) If all $\lambda_1, \lambda_2, \ldots, \lambda_k$ are negative, the static point is showing the maximum,

ii) If all $\lambda_1, \lambda_2, \ldots, \lambda_k$ are positive, the static point represents the minimum and,.

iii) If the signs of $\lambda_1, \lambda_2, \ldots, \lambda_k$ eigenvalues are mixed, the static point denotes the saddle point [8, 12, 13].

2.3. Central Composite Design

Central composite trial order (CCD) is one of the most popular methods for creating a second order response level model. The CCD is composed of 2^k number of two-level factorial trials, with 2k number of axes or star point. Also nc contains a number of central points. The factors in the model must be at least two-level. The placement of the axis points in the trial layout is given in Table 2.1. The main effects of the second order model and the first-order interaction effects are obtained from the 2^k experiment, while the curvature of the system is tested with the help of the center points. Quadratic terms in the model with the help of axis points are estimated [13, 8, 10, 12, 14].

Table 2.1. Central Composit Design

2.4. Box-Behnken Design

These experimental schemes laid out by Box and Behnken in 1980 are an effective method to create model of second order response surfaces. It is a method built on unbalanced block trials. The factors to be included in the model must have at least three levels. Let us try to explain the structure of the experiment with the help of a 3-factor experiment. In the Box-Behnken layout, the value of one of the factors is fixed at the central value and combinations of all the other factors are applied [13,8,15,16,17,18]. As can be seen in Table 2.2, combinations of all levels of A and B factors were applied at the first level of C factor. The most recent columns of the layout matrix are center point values.

Table 2.2. Three Factors Box-Behnken Desgin

3. RESULTS

Data set

The study data consisted of 40 obese patients who lost weight by bariatric surgery between February 2015 and December 2016. Body Mass Index (BMI), Age and HOMA values were evaluated in 3 categories and 3 levels, and the change in Epicardial Fat Thickness (ΔEFT) has been chosen as response variable.. The trial set-up was planned before working and the study data were determined in accordance with the trial order.

Table 3.1. Data design for three-factor design

Measurement of epicardial fat thickness: EFT was described as the echo-free area between the free wall of the myocardium and the visceral layer of the pericardium. It was measured by standard transthoracic 2D echocardiography (Vivid S5 ultrasound machine, GE, Healthcare, Horten, Norway) in the parasternal long axis views of 3 cardiac cycles at the end of the diastole and perpendicular to the right ventricular free wall as previously described [1-3]. All measurements were performed by the same investigators who were blinded to all clinical data of the patients. After digitally stored reviewed by senior echocardiographer in order to avoid inter-reader variability.

First of all, 3^3 trial designs were determined by CCD design and contour and response graphs were drawn according to the most radical increase or decrease.While planning the CCD design, 3 factors were established as $\alpha = 1{,}633$, 6 axial points, 4 central points and 2 axial central points.

Table 3.2. CCD design analysis results

When Table 3.2 is examined, the interaction effects of Age and BMI, Age and HOMA and BMI and HOMA variables were significant (p values respectively; 0.041, 0.031 and 0.026). According to these results, optimum ΔEFT combinations were determined by drawing contour and response graphs and Model Equation was expressed as 3.1. The R^2 value of the model was found as 87.75%.

The model was formed in accordance with the Equation 3.1.

$$\Delta EFT=2.03+ 0.0198\ Age+ 0.013\ BMI + 0.0078\ HOMA - 0.000481\ Age*Age - 0.00028\ BMI*BMI- 0.000282\ HOMA*HOMA + 0.000168\ Age*BMI + 0.000055\ Age*HOMA + 0.000221\ BMI*HOMA \quad (3.1)$$

Figure 3.1. Contour and response surface graphs for CCD design

As a result of CCD analysis, it was determined that the optimum EFT = 2.571 was determined as Age = 30.52, BMI = 45.30, HOMA = 34.62.

BBD design is planned as 3 factors and 3 central points.

Table 3.3. BBD design analysis results

When Table 3.3 is examined, the interaction effects of Age and BMI, Age and HOMA and BMI and HOMA variables were significant (p values respectively; 0.043, 0.040 and 0.022). In this case, contour and response graphs were drawn, optimum ΔEFT combinations were determined and Model equality was expressed at Equation 3.2.. The R^2 value of the model was found to be 91.27%.

$$\Delta EFT =-7.72 + 0.1718\ Age + 0.245\ BMI + 0.0599\ HOMA - 0.001746\ Age*Age - 0.00166\ BMI*BMI - 0.000766\ HOMA*HOMA - 0.000653\ Age*BMI + 0.000173\ Age*HOMA - 0.000690\ BMI*HOMA \quad (3.2)$$

Figure 3.2. Contour and response surface graphs for BBD experiment design

As a result of the BBD analysis, when Age = 38.36, BMI = 63.18, HOMA = 14.95, optimum ΔEFT = 3.756.

Figure 3.3. CCD and BBD design optimal point

As can be seen from Figure 3.3, there are clear optimal differences between CCD and BBD designs.

4. DISCUSSION

One of the goals of response surface studies is to determine an appropriate function (or model) to determine the relationship between the response variable and the input variables in order to accurately predict the future values of the response variable. Another is to investigate the largest or the smallest response value depending on the type of the problem and to determine the values of the input variables that can provide this value. Finally, the contribution of a mechanism to an understanding of the mechanism underlying a response system. As a result of CCD analysis, Age = 30.52, BMI = 45.30, HOMA = 34.62, the optimum ΔEFT = 2.571. As a result of the BBD analysis, Age = 38.36, BMI = 63.18, HOMA = 14.95, the optimum, ΔEFT = 3.756. Optimum Δ EFT is modeled with Contour and Response surface. According to the results of the analysis, it was found that BBD analysis for optimum ΔEFT was much more positive than CCD and optimum Age, BMI and HOMA combinations were determined to reach maximum ΔEFT.

Body mass index and waist circumference are the widely accepted measurements of generalized adiposity; however they are poor indicators for visceral obesity. It is well known that visceral adipose tissue accumulation is associated with subclinical atherosclerosis and increased cardiovascular risk more strongly than generalized adiposity [19]. Emerging data have suggested that EFT is a reliable method to assess visceral adiposity and strongly correlates with cardio-metabolic risk factors independent of overall adiposity [20,21]. EFT ≥5 mm was found to be associated with higher incidence of detectable carotid atherosclerosis [21]. In addition EFT may be a modifiable factor for CVD or a target to modify cardiovascular risk [22]. Early atherosclerotic structural changes including EFT and carotid intima media thickness may be reversed or improved by sustained weight loss following LSG in asymptomatic obese patients (5).

Patient are generally operated according to standard bariatric surgical indications in guidelines [23,24]. However which patients have more cardiovascular benefit following bariatric surgery is uncertain. Our results may be helpful to address this question. Short follow-up period is an important limitation of our study. Randomized, prospective and large scale further studies are required to confirm our results.

Ethical Standards section

Ethic Decleration

In this research article which was prepared for journal;

- We have obtained the data, information and documents in the framework of academic and ethical rules,
- We provide all the information, documents, evaluations and results in accordance with scientific ethics and moral codes,
- We referred to all of the articles I used in this study with appropriate references,
- We have not made any changes to the data used and the results,
- The information and findings specified in this study are original.

We declare above mentioned issues and accept all rights losses that may arise against me.

This study was approved by Baskent University Institutional Review Board and Ethics Committee and supported by Baskent University Research Funding (Approval number: KA16/281).

5. REFERENCES

1. Altun, A., “Optimum Verimi Sağlayan Bitki Besin Maddeleri Kombinasyonlarının Etki Yüzey (Response Surface) Metoduyla Saptanması”, Doktora Tezi, Ankara Üniversitesi Fen Bilimleri Enstitüsü, Ankara, 1-3, 22-28 (1988).

2. Altin C, Sade LE, Gezmis E, Yilmaz M, Ozen N, Muderrisoglu H. Assessment of epicardial adipose tissue and carotid/femoral intima media thickness in insulin resistance. J Cardiol 2017;69(6):843-850.

3. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-310.

4. Nelson MR, Mookadam F, Thota V, Emani U, Al Harthi M, Lester SJ, et al. Epicardial fat: an additional measurement for subclinical atherosclerosis and cardiovascular risk stratifcation? J Am Soc Echocardiogr 2011;24:339-345.

5. Altın C, Erol V, Aydın E, et al. Impact of Weight Loss on Epicardial Fat and Carotid Intima Media Thickness after Laparoscopic Sleeve Gastrectomy: A prospective study. Nutr Metab Cardiovasc Dis. 2018 May;28(5):501-509. doi: 10.1016/j.numecd.2018.02.001. Epub 2018 Feb 9.

6. Kul, S., "Cevap Yüzeyi Yöntemleri", Yüksek Lisans Tezi, Mersin Üniversitesi, Mersin, 3-16, 35-48 (2004).

7. Mead, R., Pike D.J., "A Biometrics Invited Paper, A Reviev Of Response Surface Methodology From A Biometric Viewpoint", Biometrics, 31: 803-851 (1975).

8. Doğan, İ. S., Okut, H., "As a Tool Response Surface Methodology (RSM) in a New Product Development", Itafe-03-International Congress on Information Technology in Agriculture, Food and Environment, İzmir (2003).

9. Güvenç, A., Kapucu, N., Kapucu, H., Aydoğan, Ö., Mehmetoğlu, Ü., " Enzymatic Esterification Of İsoamyl Alcohal Obtained From Fusel Oil: Optimization By Response Surface Methodology", Enzyme and Microbial Technology, 40: 778-785 (2006).

10. Schmidt, S., Launsby, R.A., Air Academy Press: Colorado Springs, Understanding Industrial Designed Experiments, 3rd Edition, , CO (1991).

11. Lucas, J.M., "How to Achieve a Robust Process Using Response Surface Methodology," Journal of Quality Technology, 26, 248-260 (1994).

12. Lawson, J.S., Madrigal, J.L.,"Robust Design Through Optimization Techniques," Qualify Engineering, 6: 593-608 (1994).

13. Alexander, M. T., "Response Surface Optimization Using Jmp Software", SAS Conference Proceedings: SAS Users Group International, San Diego, California, 841-847 (1997).

14. Özler, C. "Optimum Toleransların Belirlenmesinde Cevap Yüzeyi Yöntemlerinin Kullanılması Üzerine Bir İnceleme", D.E.Ü.İ.İ.B.F. Dergisi, 21: 71-83 (2006).

15. Myers, R. H., Montgomery D.C., "Response Surface Methodology Process And Product Optimization Using Designed Experiments", John Wiley and Sons, 17-85, 203-303 (2002).

16. Montgomery, D.C., “Design And Analysis Of Experiments”, John Wiley and Sons 427-510 (2001).

17. Tekindal M.A., Bayrak H, Ozkaya B, YavuzG., Box- Behnken Experimental Design in Factorial Experiments: The Importanceof Bread for Nutrition and Health, Turkish Journal of Field Crops, Volume: 17,No:2, page:115-123 2012

18. Tekindal M.A., Bayrak H, Ozkaya B, YavuzY, Second-order response surface method: factorial experiments an alternativemethod in the field of agronomy, Turkish Journal Of Field Crops 2014, Volume: 19 Issue: 1 Pages: 35-45

19. Natale F, Tedesco MA, Mocerino R, de Simone V, Di Marco GM, Aronne L, et al. Visceral adiposity and arterial stiffness: Echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives. Eur J Echocardiogr 2009;10:549-555.

20. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-310.

21. Nelson MR, Mookadam F, Thota V, Emani U, Al Harthi M, Lester SJ, et al. Epicardial fat: an additional measurement for subclinical atherosclerosis and cardiovascular risk stratifcation? J Am Soc Echocardiogr 2011;24:339-345.

22. Rabkin SW, Campbell H. Comparison of reducing epicardial fat by exercise, diet or bariatric surgery weight loss strategies: a systematic review and meta-analysis. Obes Rev 2015;16(5):406-15.

23. Rosenthal RJ; International Sleeve Gastrectomy Expert Panel, Diaz AA, Arvidsson D, Baker RS, Basso N, Bellanger D, et al. International Sleeve Gastrectomy Expert Panel Consensus Statement: Best practice guidelines based on experience of>12,000 cases. Surg Obes Relat Dis 2012;8:8-19.

24. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. International Federation for Surgery of obesity and metabolic disorders-European chapter (IFSO-EC); European Association for the Study of obesity (EASO); European Association for the Study of Obesity Obesity Management Task Force (EASO OMTF). Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg 2014;24(1):42–55.

Figures

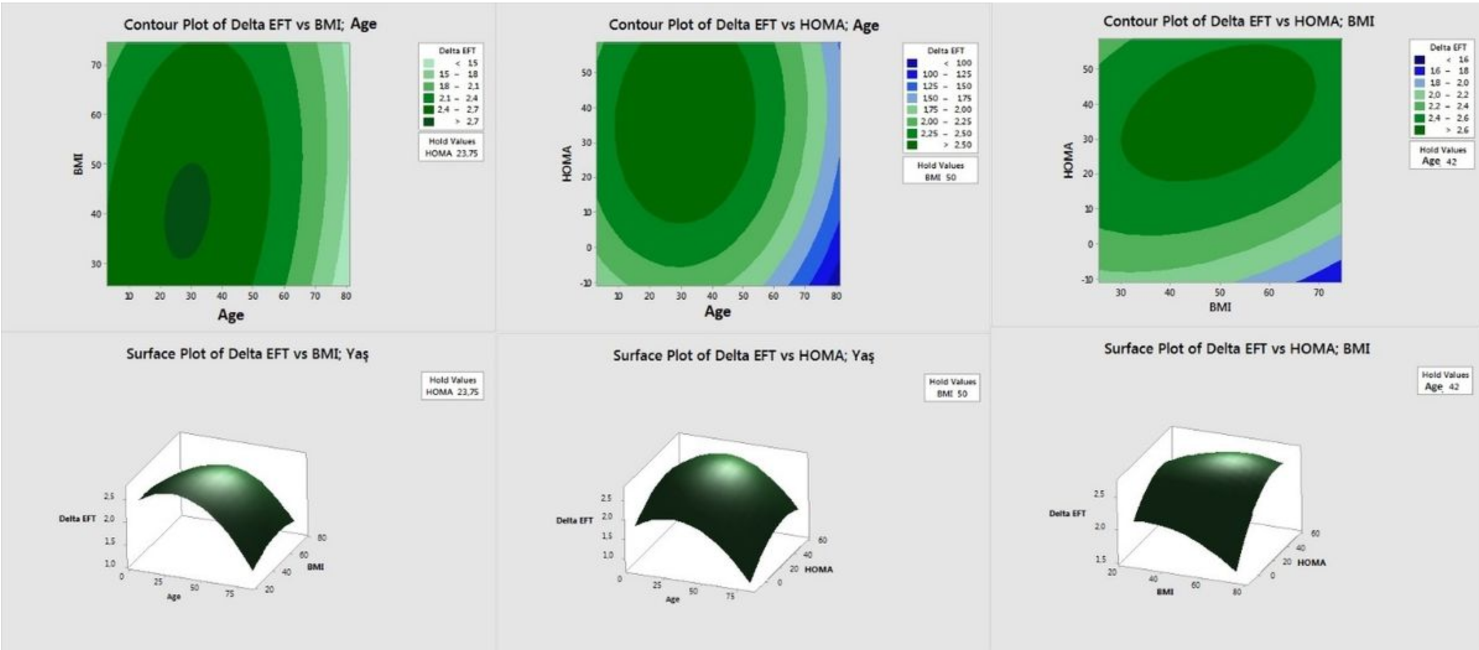

Figure 1

Contour and response surface graphs for CCD design

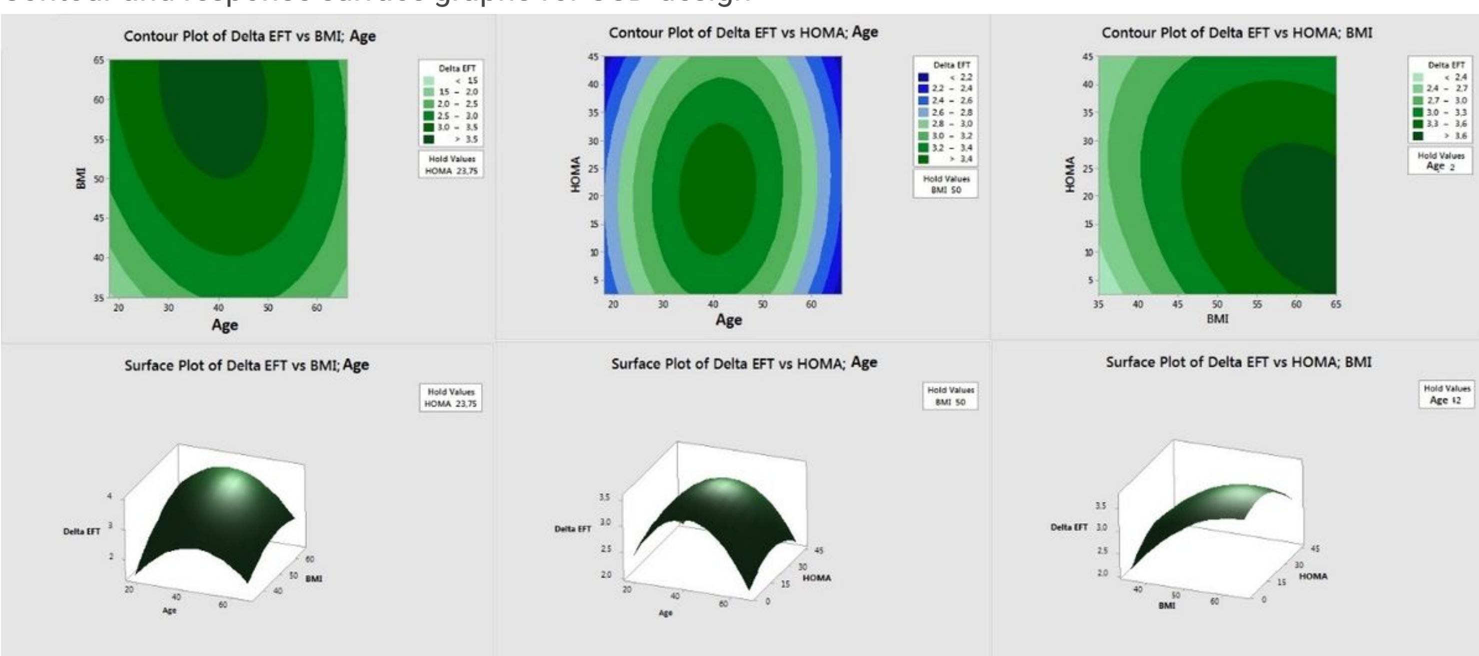

Figure 2

Contour and response surface graphs for BBD experiment design

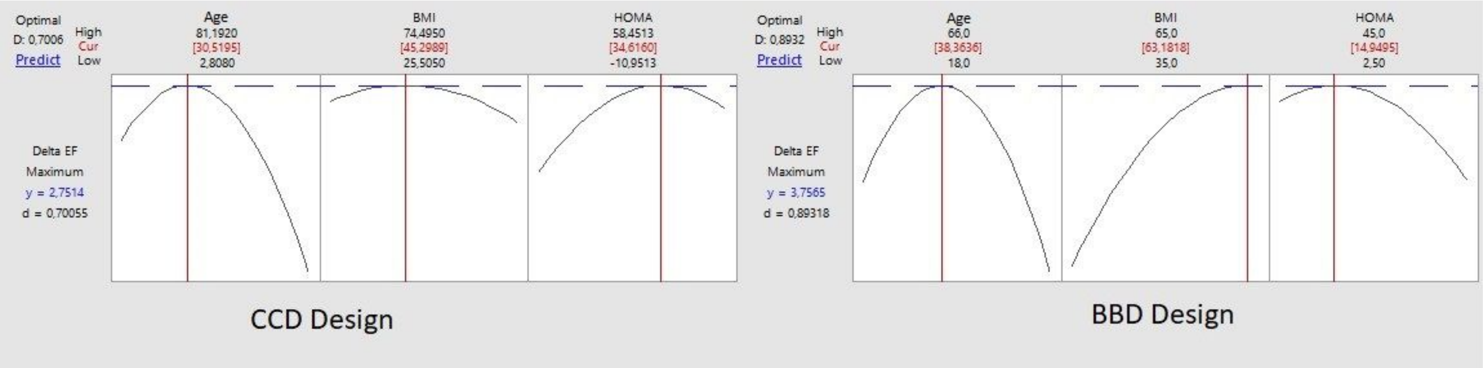

Figure 3

CCD and BBD design optimal point