Impact Of Oral Health Related Quality Of Life And Possible Role Of Self-Esteem In Orthodontic Patients: A Prospective Clinical Study

Prasad Mandava1*, Surendra Gangavarapu2, GowriSankar Singaraju1, Venkatesh Nettam4, Sindhu Chandrika P5, Aparna Palla6

1 Professor and Head, Orthodontics, Narayana Dental College and Hospital, Nellore, AP, India.
2 Postgraduate Student, Orthodontics, Narayana Dental College and Hospital, Nellore, AP, India.
3 Professor, Orthodontics, Narayana Dental College and Hospital, Nellore, AP, India.
4 Senior Lecturer, Orthodontics, Narayana Dental College and Hospital, Nellore, AP, India.
5 Assistant professor, Government Dental College and Hospital, Kadapa, Nellore, AP, India.
6 Professor, Orthodontics, college of dental sciences, Davangere, India.

Abstract

The study aimed to evaluate the relationship between oral health-related quality of life (OHRQoL) concerning self-esteem reports in children before, during and after orthodontic treatment. This prospective clinical study included 139 patients between 11-16 years old (66 boys and 73 girls) and requested to complete the questionnaires before the start of treatment (T0), one year after the start of treatment (T1), and at two months retention follow up (T2). One-way analysis of variance (ANOVA) was used for comparisons between the pre, mid and post-treatment means of the study group and to study the significance of changes in parameters over time (for both OHRQoL and SE measures). Pairwise comparison between the individual groups was made Post – hoc Scheffe test. Spearman’s rank-order correlation coefficient (ρ) was used to evaluate the association between the two ordinal variables. The level of significance was set at a p-value of 0.05 for all tests. The mean value for overall OHRQoL was increased at mid-treatment and decreased at post-treatment, which is significant (p<0.001). The mean value for overall self-esteem was decreased at mid-treatment and post-treatment, which is also significant (p<0.001). Oral health-related quality of life increased after orthodontic treatment compared to mid-treatment but comparatively less than at pre-treatment, which is statistically significant. The impact on OHRQoL increases during and after orthodontic treatment, and the self-esteem decreased during and after orthodontic treatment.

Keywords: Child Perception Questionnaire; Oral Health-Related Quality Of Life; Orthodontic Treatment; Self-Esteem.

Introduction

The goal of orthodontic treatment is to improve the quality of life of patients by enhancing dental, jaw function and dentofacial aesthetics. The modern health care paradigm has shifted towards the quality of life in the last decade. The impact of oral health on the quality of life is measured by endogenous, functional, social or psychological determinants and is usually known in the literature as OHRQoL – the oral health-related quality of life.

Quality of life can be determined as ‘a person’s sense of well-being, which stems from satisfaction or dissatisfaction with the areas of life that are important to him or her.’[1] Oral health-related quality of life (OHRQoL) is defined as the absence of negative impacts of oral conditions on social life and a positive sense of dentofacial self-confidence.[2] The concept of oral health-related quality-of-life (OHRQoL) has become increasingly more important in oral health practice and research. In orthodontics, with a shift from a more traditional biomedical model towards a more biopsychosocial model, the interest in oral health-related quality of life (OHRQoL) also has increased considerably.[3]

Oral health-related quality of life is a multidimensional concept that includes subjective evaluation of perceived physical, psychological and social aspects of oral health and no single measure has been developed that captures the concept completely. Both

*Corresponding Author:
Dr. Mandava Prasad MDs, FPFA, FICD (U.A.),
Sr. Professor & Head, Department of Orthodontics and Dentofacial Orthopedics, Narayana Dental College and Hospital, Chinthareddypalem, Nellore – 524002, Andhra Pradesh, India.
Tel: 09440976666
E-mail: mandavabruno9@gmail.com

Received: September 07, 2021
Accepted: November 28, 2021
Published: December 07, 2021

Citation: Prasad Mandava, Surendra Gangavarapu, GowriSankar Singaraju, Venkatesh Nettam, Sindhu Chandrika P, Aparna Palla. Impact Of Oral Health Related Quality Of Life And Possible Role Of Self-Esteem In Orthodontic Patients: A Prospective Clinical Study. Int J Dentistry Oral Sci. 2021;8(12):5185-5190.

Copyright: Dr. Mandava Prasad MDs, FPFA, FICD©2021. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.
generic and disease-specific measures had been used to measure health and oral health-related quality of life.[4, 5]

Self-esteem (S.E.) can be defined as the perception of one's own ability to master or deal effectively with the environment and is affected by the reactions of others towards an individual [6]. Self-concept is broad-ranging and relates to personal self-concept (facts or one's own opinions about oneself), social self-concept (one's perceptions about how one is regarded by others), and self-ideals (what or how one would like to be). [3]

A malocclusion does affect physical, social, and psychological functioning, which can be defined as 'quality of life.' [6] OHRQoL can help us understand the demand for orthodontic treatment beyond clinical parameters and sheds stumbles across the effects of malocclusion on people's lives. [7] The literature proposes that studies on OHRQoL concerning malocclusion have reported higher levels of oral impact in patients with severe malocclusion compared with a normal population and the treatment of severe malocclusion reduced the reported oral impacts to the level of the general population and significantly improved oral health-related quality of life. [8, 9] Hassan and co-workers [7] also found an impact of malocclusion on oral health-related quality of life of young adults. Furthermore, the subjects with more severe malocclusion and dentofacial deformities are more likely to report oral impacts than those with milder malocclusion. [10]

The impact of malocclusion differs between genders and age groups. Studies have indicated that females experience poorer OHRQoL than males. This gender difference in malocclusion perception could be because females pay more attention to their appearance and refer to orthodontic clinics more often than males [11]. In a study of Brazilian school children, those with low S.E. were found to be more sensitive to the aesthetic effects of malocclusion. [12] The relationship between normative measures of malocclusion, S.E., and OHRQoL was studied by Agou et al. [3] using OHRQoL outcomes in children seeking orthodontic treatment and hypothesized that children with high S.E. would have better OHRQoL than those with low S.E. Likewise, a study of potential orthodontic patients in Nigeria found that children with high S.E. most frequently did not express orthodontic concerns. [13]

Various studies investigated the effect of psychological aspects during orthodontic treatment between treated patients and untreated control groups. [14, 15] Seeing that an unattractive dentition has been associated with teasing, bullying, and negative OHRQoL impacts. Differences between treated and untreated subjects are anticipated in light of studies emphasizing the importance of dentofacial esthetics in daily social interactions. [16-18] Thus improving dental esthetics and, subsequently, psychological well-being is frequently stated reasons for seeking orthodontic treatment during childhood and adolescence. [1, 19]

A recent cross-sectional study at the baseline by De Baets et al. [20] was performed to investigate whether a relationship exists between orthodontic treatment need and OHRQoL and whether this relationship is influenced by Self-esteem (S.E.). On the continuation of a baseline study, Broussier et al. [6] conducted a follow-up study to investigate the changes of OHRQoL and the influence of Self-esteem during the mid-treatment phase, one year after the start of orthodontic treatment and hypothesized that OHRQoL deteriorates during orthodontic treatment. Further they stated that self-esteem can be a protective factor in OHRQoL during orthodontic treatment.

Although there has been extensive research concerning the topic of OHRQoL, the focus of most research projects was children. [6, 9, 20] Only a few prospective studies have been published concerning the effect of a change in occlusion on the OHRQoL. To our knowledge, there is no published research using C.P.Q and SPPA on Indian patients. This has encouraged us to carry out this study to obtain the baseline information for the Indian population. Therefore, the present study was made to explore the changes of OHRQoL and the possible role of self-esteem in children before, during, and after the completion of orthodontic treatment.

The study was conducted to assess (a) the OHRQoL reports in children before, during and after orthodontic treatment, (b) to estimate the Self-esteem reports in children before, during and after orthodontic treatment and (c) to compare and correlate the association between OHRQoL and Self-esteem in children before, during and after orthodontic treatment.

Materials And Methods

Study Design

The present prospective study was approved by the institutional ethics committee, Naryana Dental College and Hospital, Nellore (NDC/IECC/2014-15/070 dt.31/12/2014). Informed consent was obtained from all participants or where appropriate one of their parents or caretakers after explaining the procedure in English or their native language.

A total of 139 patients between 12-16 years old (66 boys and 73 girls) and requested to complete the questionnaire before the start of treatment (T0). This study group was monitored throughout the orthodontic treatment are requested to complete the same questionnaire 3 months after the start of treatment (T1) and at two months retention follow up (T2). Eight discontinued in between treatment due to various reasons and five patients did not turn up after two months retention follow up. So only 126 patients were evaluated for the questionnaire given at three points of time. Twelve patients submitted incompletely filled questionnaires at one or the other point of time. This resulted in a final study group of 114 patients (52 boys and 62 girls), who filled the questionnaire at all three time periods required in this study. The study flow chart describes the design of the study (Figure 1). Thus the statistical analysis is done for this final study group (n=114). The response rate is 82% which is sufficient for analyzing the data.

Patients who had no history of previous orthodontic treatment, with good physical and mental health and with fixed appliance therapy were selected for this study. Subjects who exhibited severe medical problems like mental and physical problems, children with severe malocclusions like cleft lip and palate, orthopedic appliances, myofunctional and other removable appliances were excluded from the study.

Every healthy child registered for first orthodontic treatment at the Department of Orthodontics was requested to complete the
The oral health-related quality of life (OHRQoL) of the child was scored by using the original English or Telugu translation of the child perception questionnaire (C.P.Q11-14) [21] has already been validated in orthodontic research. It contains 37 questions about the frequency of events at 4 domains.

Self-esteem of the child will be assessed by using the original English or Telugu translation of the Harter's self-perception profile for adolescents (SPPA) [22], which consists of 35 questions designed to discover the adolescent perception of themselves in 7 different domains. In line with our baseline study, 'sense of dignity' was considered as a measure of global Self-esteem.[23]

A detailed scoring key for this format was also provided in the manual by S Harter [22]. Each of the seven subscales contains five items, constituting a total of 35 items.

Statistical Analysis was performed using SPSS (Statistical Package for the Social Sciences, version 21, Armonk, NY: I.B.M. Corp.). Basic demographic data were expressed in means ± standard deviations. The categorical data were converted to numerical scoring and the Statistical test, ANOVA was used for comparisons between the pre, mid and post-treatment means of the study group and to study the significance of changes in parameters over time (for both OHRQoL and S.E. measures). A pairwise comparison between the individual groups was done 'Post – hoc Scheffe test'. Spearman's rank-order correlation coefficient (ρ) was used to evaluate the association between the two ordinal variables. The level of significance was set at p < 0.05 for all tests.

Results

Table 1 shows the mean C.P.Q. scores for each domain were increased at one year after starting treatment (T1) whereas scores are decreased after treatment (T2). Post – hoc scheffe's test was done for pairwise comparisons between pre (T0), mid (T1) and post-treatment (T2) of significant domains of the "C.P.Q." questionnaire.

Table 2 shows the total 'C.P.Q.' and 'SPPA' scores for overall OHRQoL and overall Self-esteem. The mean value for overall OHRQoL was increased at mid-treatment and decreased at post-treatment which is significant (p<0.001). The mean value for overall Self-esteem was decreased at mid-treatment and post-treatment which is also significant (p<0.001). Post-Hoc Scheffe's test was done for multiple comparisons between pre (T0), mid (T1) and post-treatment (T2) of overall "C.P.Q." and "SPPA" scores (Table-3).

The correlation between the quality of life and Self-esteem at pre (T0), mid (T1) and post-treatment time (T2) using spearman's rank-order correlation coefficient (Table-4). The results showed a weak negative correlation between total OHRQoL (C.P.Q.) and S.E. at T0 (ρ=-0.167, p=0.075), T1 (ρ=-0.204, p=0.03) and positive correlation at T2 (ρ=0.193, p=0.04).

The correlation between the quality of life and Self-esteem was assessed for total treatment time using spearman's rank-order correlation coefficient. The results showed a weak negative correlation between total OHRQOL (C.P.Q.) and S.E. (ρ = -0.092) which is non-significant (p>0.05) (Table-5).

Discussion

The OHRQoL measure used in this study is the CPQ11−14. Because of its definite psychometric properties, the CPQ11−14 is a useful measure for orthodontic trials and has become a popular tool in orthodontic outcome research [4, 24, 25]. The use of this instrument is validated for the agegroup 11−14 years, but in our study, we also included 15- to16-year-old subjects. Furthermore, some authors question whether C.P.Q. is a good measure of OHRQoL in children with malocclusions. Anyway, some criticism of subjective measures such as OHRQoL has to be taken into account: people may adapt or habituate to their (health) conditions over time and they may respond with lower impact scores when a questionnaire is re-administered at a later time[4,26]Bennabetti al. [27] found a different pattern of sociodental impact by type of appliance. Subjects wearing fixed appliances had a higher frequency of impact than those wearing removable or both types of appliances.
Table 1. Pair wise comparison; domain scores for the child perception questionnaire [CPQ11-14] in Oral Health Related Quality of Life at different time periods of treatment- Post-hoc Scheffé test.

| Domain         | Groups              | T-statistic | p value  |
|----------------|---------------------|-------------|----------|
| Oral Symptoms  | Pre v/s Mid         | 4.308       | <0.01*   |
|                | Pre v/s Post        | 0.060       | 0.998Ns  |
|                | Mid v/s Post        | 4.369       | <0.01*   |
| Functional Limitations | Pre v/s Mid | 5.010       | <0.01*   |
|                | Pre v/s Post        | 2.505       | <0.05*   |
|                | Mid v/s Post        | 2.505       | <0.05*   |
| Social Well-being | Pre v/s Mid     | 3.522       | <0.01*   |
|                | Pre v/s Post        | 0.710       | 0.777Ns  |
|                | Mid v/s Post        | 2.812       | <0.05*   |

** P< 0.01- Highly significant; * P< 0.05- Significant; Ns P> 0.05- Non significant;

Table 2. Total scores for overall changes in oral health related quality (OHRQoL) of life and Self- esteem (SE) - “ANOVA” test.

| Measure          | Groups                        | Sample size (n) | Mean ± SD | F value | p value |
|------------------|-------------------------------|-----------------|-----------|---------|---------|
| Overall Pre treatment | 114                       | 41.07 ± 19.48   | 8.01      | < 0.001** |
| Quality of Life Mid treatment | 114                    | 54.21 ± 29.18   | 8.007     | < 0.01*   |
| Post treatment   | 114                          | 43.94 ± 16.27   | 10.873    | < 0.001** |
| Overall Post treatment | 114                     | 93.12 ± 8.07    |           |         |
| Self- esteem Mid treatment | 114              | 91.71 ± 7.43    | 3.711     | <0.01*   |
| Post treatment   | 114                          | 89.57 ± 3.79    |           |         |

** P< 0.001- Highly significant; * P< 0.05- Significant; Ns P> 0.05- Non significant;

Table 3. Pair wise comparison; overall OHRQoL and overall Self- Esteem measures at different time periods- ‘Post-hoc Scheffe test’.

| Measure          | Comparison                  | T-statistic | p value  |
|------------------|-----------------------------|-------------|----------|
| Overall Pre v/s Mid | 4.296                    | <0.01*   |
| Quality of Life Pre v/s Mid | 8.007        | <0.01*   |
| Mid v/s Post      | 3.711                      | <0.01*   |
| Overall Pre v/s Mid | 1.580                    | 0.288Ns |
| Self- esteem Pre v/s Post | 3.971       | <0.01*   |
| Mid v/s Post      | 2.390                      | 0.058Ns |

** P< 0.001- Highly significant; * P< 0.05- Significant; Ns P> 0.05- Non significant;

Table 4. Spearman rank correlation coefficients for comparison of total OHRQoL, individual domain of OHRQoL and SE (At T0, T1, T2):

| Parameters          | T0                  | T1                  | T2                  |
|---------------------|---------------------|---------------------|---------------------|
|                    | 'ρ'Value | P Value | 'ρ'Value | P Value | 'ρ'Value | P Value |
| Total OHRQoL SE     | -0.167               | 0.075              | -0.204             | 0.031*               | 0.193             | 0.041*               |
| OS                  | -0.048               | 0.609              | -0.261             | 0.005*               | 0.152             | 0.105               |
| FL                  | -0.026               | 0.028*             | -0.19              | 0.043*               | -0.048             | 0.61               |
| EW                  | -0.11                | 0.242              | -0.109             | 0.251                | 0.315             | 0.001**            |
| SW                  | -0.17                | 0.07               | -0.174             | 0.064                | 0.251             | 0.008*             |

** P< 0.001- Highly significant; * P< 0.05- Significant; Ns P> 0.05- Non significant; 
T0 - Pre treatment; T1 - Mid treatment; T2 - Post treatment; 'ρ' - Rho value;
Table 5. Spearman rank correlation coefficients for comparison of total OHRQoL, individual domain of OHRQoL and SE (Total treatment time).

| Parameters                   | Rho (ρ) Value | P Value     |
|------------------------------|---------------|-------------|
| Total OHRQoL (CPQ)           | -0.092        | 0.092 Ns    |
| Oral Symptoms (OS)           | 0.046         | 0.398 Ns    |
| Functional Limitation (FL)   | -0.167        | 0.002**     |
| Emotional Well-being (EW)    | 0.003         | 0.953 Ns    |
| Social Well-being (SW)       | -0.075        | 0.169 Ns    |

** P < 0.001-Highly significant; * P < 0.05- Significant; Ns P > 0.05- Non significant;

Finally, it is important to reconsider the current biomedical and restricted paradigm on OHRQoL and to begin to think about the series of processes by which social and psychological factors influence OHRQoL reports [28]. According to the model of Wilson – Clearly, also biological variables, health perception biological variables, symptom status, healthy functioning, and other (psychosocial) factors need to be taken into consideration [29].

In recent times, Baker and co-workers [30] demonstrated that sense of coherence was the most important psychosocial predictor for OHRQoL. For instance, the direct contribution of factors such as other oral health problems was not assessed in this investigation. A recent study by M.clijmans and co-workers [31] suggests that orthodontic treatment need, S.E., and some personality traits influence OHRQoL. Like the present study, a moderating role cannot be confirmed.

Some limitations regarding this study also needed to be considered. The results of the present study demonstrated the comparison and correlation of OHRQoL and S.E. in the patients who had come to the clinic and taken orthodontic treatment. The question leftovers whether these correlations are still present in the general population, and this aspect needs to be evaluated.

According to the literature, we expect that the OHRQoL will change during treatment, but the association between OHRQoL and S.E. depicts a weak correlation in the present study. The question remains what the influence is of psychological factors such as S.E. and personality traits, other psychosocial factors.

This study has not differentiated gender-wise comparisons; the socioeconomic status of the subjects at baseline level was not considered, and patients with only fixed appliances were found in the present study.

Hence, further work should be attempted with larger samples, different age groups, different gender, and longer follow-ups to sort out the role of these factors on the outcome of orthodontic treatment and the use of OHRQoL measures as validation for orthodontic treatment. OHRQoL can provide evidence that costs associated with treatment are worth the expense and can help the patient in their decision making. Besides, professionals can weigh the risks and benefits associated with treatment more accurately [32].

Conclusion

- OHRQoL for total, oral symptoms, functional limitations, and social well-being domains deteriorate during and after orthodontic treatment.
- Total OHRQoL (for oral symptoms, functional limitations, and social well-being domains) decreased during the mid-orthodontic treatment compared to pre-treatment and then increased after orthodontic treatment compared to mid-treatment but comparatively less than at pre-treatment which is statistically significant.
- OHRQoL changes for oral symptoms, social well-being domains were not evident when compared that at pre and post-treatment.
- Total S.E. also decreased during and after orthodontic treatment when compared to that at pre-treatment.
- The correlation between OHRQoL and S.E. measured was weak. However, as the impact on OHRQoL increases (high CPQ score) during and after orthodontic treatment, the S.E. was decreased during and after orthodontic treatment.

Authors Contribution

Concept- Dr Prasad Mandava, Dr Surendra Gangavarapu, Design – Dr Prasad Mandava, Dr Gowri Sankar Singaraju, Data Collection and Processing- Dr Surendra Ganagavarapu, Dr Venkatesh Nettam, Analysis and Interpretation- Dr P Sinduchandrika, Dr Surendra Gangavarapu, Literature Search- Dr Aparna Palla, Dr PSinduChandrika, Writing manuscript- Dr Mandava Prasad, Dr GowriSankarSingaraju, Critical Review- Dr Mandava Prasad, Dr Aparna Palla

References

[1]. Cunningham SJ, Hunt NP. Quality of life and its importance in orthodontics. J Orthod. 2001 Jun;28(2):152-8. PubMed PMID: 11395531.
[2]. Inglehart M, Bagrnanian R. Oral health-related quality of life. Chicago: Quintessence; 2002:1-6.
[3]. Agou S, Locker D, Streiner DL, Tompson B. Impact of self-esteem on the oral-health-related quality of life of children with malocclusion. Am J OrthodDentoFacialOrthop. 2008 Oct;134(4):484-9. PubMed PMID: 18929265.
[4]. Locker D, Allen E. What do measures of ‘oral health-related quality of life’ measure? Community Dent Oral Epidemiol. 2007 Dec;35(6):401-11. PubMed PMID: 18059281.
[5]. Allen PF, McMillan AS, Walshaw D, Locker D. A comparison of the validity of generic- and disease-specific measures in the assessment of oral health-related quality of life. Community Dent Oral Epidemiol. 1999 Oct;27(5):344-52. PubMed PMID: 10505795.
[6]. Brossen V, Ghijselings I, Jürgenlumiere, Steffenfiez, Maitelcilmans, Willems G. Changes in oral health-related quality of life in children during orthodontics treatment and the influence of SE. Eur J Orthod. 2014;
discriminating individuals who seek orthodontic treatment. J Dent Res. 1981 Sep;60(9):1661-7. PubMed PMID: 6943159.

[20]. De Baets E, Lambrechts H, Lemiere J, Diya L, Willems G. Impact of self-esteem on the relationship between orthodontic treatment need and oral health-related quality of life in 11- to 16-year-old children. Eur J Orthod. 2012 Dec;34(6):731-7. PubMed PMID: 21750244.

[21]. Jokovic A, Locker D, Stephens M, Kenny D, Tompson B, Guyatt G. Validity and reliability of a questionnaire for measuring child oral-health-related quality of life. J Dent Res. 2002 Jul;81(7):459-63. PubMed PMID: 12161456.

[22]. Harter S. Manual for the self-perception profile for adolescents. University of Denver, Denver. 1988.

[23]. Hagborg WJ, The Rosenberg Self-Esteem Scale and Harter’s Self-Perception Profile for Adolescents: a Concurrent Validity Study. Psychol Sch. 1993;30(2):132–6.

[24]. O’Brien K, Wright JL, Conboy F, Macfarlane T, Mandall N. The child perception questionnaire is valid for malocclusions in the United Kingdom. Am J OrthodDentofacialOrthop. 2006 Apr;129(4):536-40. PubMed PMID: 16627180.

[25]. Foster Page LA, Thomson WM, Jokovic A, Locker D. Validation of the Child Perceptions Questionnaire (CPQ 11-14). J Dent Res. 2005 Jul;84(7):649-52. PubMed PMID: 15972595.

[26]. Marshman Z, Gibson BJ, Benson PE. Is the short-form Child Perceptions Questionnaire meaningful and relevant to children with malocclusion in the UK? J Orthod. 2010 Mar;37(1):29-36. PubMed Erratum in: J Orthod. 2010 Jun;37(2):140. PMID: 20439924.

[27]. Bernaèb E, Sheiham A, de Oliveira CM. Impacts on daily performances related to wearing orthodontic appliances. Angle Orthod. 2008 May;78(3):482-6. doi: 10.2319/050207-212.1. PMID: 18416624.

[28]. Lerner DJ, Levine S. Health-related quality of life: origins, gaps and directions. Adv Med Sociol.1994;5:43-65.

[29]. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: A conceptual model of patient outcomes. JAMA. 1995 Jan 4;273(1):59-65. PubMed PMID: 7996652.

[30]. Baker SR, Mat A, Robinson PG. What psychosocial factors influence adolescents’ oral health? J Dent Res. 2010 Nov;89(11):1230-5. PubMed PMID: 20759689.

[31]. Clijmans M, Lemiere J, Fieuvet S, Willems G. Impact of self-esteem and personality traits on the association between orthodontic treatment need and oral health-related quality of life in adults seeking orthodontic treatment. Eur J Orthod. 2015 Dec;37(6):643-50. PubMed PMID: 25700991.

[32]. Sischo L, Broder HL. Oral health-related quality of life: what, why, how, and future implications. J Dent Res. 2011 Nov;90(11):1264-70. PubMed PMID: 21422477.