

The Physiological, Biochemical and Quality of Life Changes in Chronic Diabetic Foot Ulcer after Hyperbaric Oxygen Therapy

MOHD YAZID B¹, AYESYAH A¹, NURHANANI AB¹, MOHD ROHAIZAT H²

¹Department of Orthopaedics and Traumatology, ²Department of Community Health Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia.

ABSTRAK

Terapi Oksigen Hiperbaric (TOH) dikesan dapat meningkatkan pengoksigenan dan kesan anti-mikrob yang berpotensi meningkatkan penyembuhan ulser kronik. Kajian ini bertujuan menilai kesan TOH dalam ulser kaki diabetik (UKD) yang kronik. Seramai enam puluh pesakit dikelaskan mengikut Wagner 1, 2 atau 3 ulser kaki diabetik kronik dan dibahagikan secara rawak kepada dua kumpulan; TOH dan kawalan. Semua pesakit menjalani rawatan piawai untuk UKD, tetapi bagi kumpulan TOH menjalani 20 sesi TOH, yang berlangsung selama 80 - 90 minit pada 2.5 atmosfera mutlak (ATA) setiap sesi. Bilangan sel putih dan tahap protein C-reaktif telah diambil semasa kemasukan wad, pada minggu kedua dan keempat rawatan. Saiz luka didokumentasikan pada setiap susulan sehingga enam bulan susulan. Soal selidik SF-36 selepas pesakit menjalani terapi oksigen hiperbarik telah digunakan untuk mengukur kualiti kehidupan dan kesihatan. Pengurangan sel putih dan protin C-reaktif dalam kumpulan TOH adalah ketara sepanjang rawatan berbanding kumpulan kawalan ($p = 0.046$ dan $p = 0.039$ masing-masing). Seramai 26 pesakit (86.7%) daripada kumpulan TOH telah mencapai penyembuhan ulser pada enam bulan susulan, manakala hanya 18 pesakit (60%) dalam kumpulan kawalan telah sembuh sepenuhnya pada enam bulan susulan. Pesakit yang dirawat dengan TOH menunjukkan konstituen kesihatan mental dan fizikal jauh lebih baik dalam soal selidik kualiti kehidupan. Adalah ditekankan bahawa TOH adalah terapi tambahan kepada rawatan ulser kaki diabetik yang kronik dalam mempercepatkan penyembuhan luka bagi memastikan kualiti hidup pesakit yang lebih baik.

Kata kunci: pengoksigenan, kualiti kehidupan, penyembuhan luka

Address for correspondence and reprint requests: Mohd Yazid Bajuri. Department of Orthopaedics and Traumatology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000, Cheras, Kuala Lumpur, Malaysia. Tel: +603-91456031 Fax: +603-91456674 E-mail:ezeds007@yahoo.com.my

ABSTRACT

Hyperbaric oxygen therapy (HBOT) was established to increase oxygenation and antimicrobial effect that potentially improve the healing of chronic ulcer. Present study aim to assess the effects of HBOT in chronic diabetic foot ulcer (DFU). A total of sixty patients classified according to Wagner 1, 2 or 3 chronic diabetic foot ulcers, were recruited and subsequently divided randomly into two groups; HBOT and control group. All patients underwent the standard treatment for DFU, but for the HBOT group, underwent 20 HBOT sessions, each lasted 80 – 90 mins at 2.5 atmospheres absolute (ATA). White cell count (WCC) and C-reactive protein (CRP) levels were taken during inclusion, at second and fourth week of treatment. Wound sizes were documented at each follow up until six months follow up. SF-36 at one-month post hyperbaric oxygen therapy was used to measure the health-related quality of life. Reduction of WCC and CRP in HBOT group were significant throughout the treatment ($p=0.046$ and $p=0.039$, respectively). A total of 26 patients (86.7%) from the HBOT group achieved complete ulcer healing at six months' follow-up, while 18 patients (60%) in the control group's ulcer healed completely. Patients treated with HBOT had significantly better mental and physical health constituent of quality of life. It must be emphasised that HBOT is an adjunctive therapy to the standard management of chronic DFU in accelerating wound healing for a better quality of life.

Keywords: oxygenation, quality of life, wound healing

INTRODUCTION

Preceding published researches of health-related quality of life (QOL) have shown distinct low quality of life in patients suffering from diabetic foot problems (Kinmond et al. 2003; Ribu & Wahl 2004). These patients experience relentless constraint on daily life basis due to the ulcer. These patients are often rendered helpless haunted by concern for the future, greater frustration with their lives, higher levels of depression and poorer psychosocial adjustment to illness (Kinmond et al. 2003; Ribu & Wahl 2004). Fejfarová et al. (2014) noted that

patients with diabetic foot problems, in particularly those with previous major amputation history, have worse quality of life in the environment domain such as financial, quality and standard of living with worse stress readaptation ability. It is believed that late complications often affect patients by hindering social interactions hence, isolation, unemployment as a results of reduce mobility and ultimately results in financial problems (Herber et al. 2007; Goodridge et al. 2005).

Cellular processes in stages of wound healing such as cell metabolism, proliferation, and revascularization crucially requires oxygen. Systemic

hyperbaric oxygen therapy (HBOT) was suggested to improve long term healing in chronic diabetic ulcers that have not improved with pertinent therapy (Lipsky & Berendt 2010). Oxygen therapy has demonstrated a vital role in increased antimicrobial activity, synthesis of collagen that enhances wound tensile strength and growth factor signal transduction (Eggleton et al. 2015). Furthermore, not only that it enhances neutrophil killing ability, hyperbaric oxygen also reduces local inflammation during revascularization of wound tissue by hindering inflammatory cell (neutrophil)-endothelial cell interaction (Eggleton et al. 2015; Kendall et al. 2013).

HBOT augments the apoptosis of phagocytes which interrupts the build-up of potentially necrotic cell debris (Almzaiel et al. 2013).

Apart from that, it also encourages angiogenesis and augment fibroblast activity (Kranke et al. 2004; Barnes 2006). Theoretically, HBOT appears to enhance the healing of ischemic foot ulcers in diabetic patients.

Londahl et al. (2010) conducted a randomized controlled trial of a total of 94 patients with Wagner grade 2, 3 or 4 ulcer were recruited. A total of 57% of these patients receiving HBOT had healed ulcer at 1-year follow up, while in the placebo group, only 29% had achieve healing. Hyperbaric sessions were conducted for 8 to 10 weeks (40 sessions in total, each session was 90 minutes at 2.5 ATA). The main aim was healed ulcer with complete epithelial regeneration. Patients divided randomly into two treatment groups were similar at initial study. More than

half had undergone vascular surgery for lower limb affected.

Generally, there was no study that correlated the effects of hyperbaric oxygen therapy with patients' quality of life. The present study aimed to assess the effects of HBOT in chronic DFU in terms of inflammatory markers, wound size reduction and quality of life.

MATERIALS & METHODS

Present study was prospective, randomised control and was conducted in a tertiary hospital. Patients were selected from June 2013 to December 2014. The selected patients were the ones who were admitted due to diabetic foot problems.

Inclusion criteria for this study were patients diagnosed with Diabetes Mellitus type 1 or 2, and had an ulcer at the foot or ankle for at least four weeks of duration. Ulcers were classified using Wagner classifications system, and only type 1, 2 or 3 were included. Patients with active infections were also included. Exclusion criteria were patients who were contraindicated for HBOT (e.g. chronic obstructive airway disease, middle ear infection etc.), patients diagnosed with critical limb ischaemia and patients who were pregnant or below 18 years of age. Patients who had severe medical illnesses that could influence the quality of life and had underwent lower limbs major amputation (level Syme's and above) were also excluded from this study.

Both informed and written consent were obtained from patients who

fitted the criteria and agreed to be included in the study. Monofilament and ankle brachial pressure index was done to gauge the severity of peripheral neuropathy and peripheral arterial disease. The size of ulcers and level of inflammatory markers were documented at initial presentation and at two and four weeks' review. All patients were required to fill-out the SF-36 questionnaires after four weeks of treatment. SF-36, a self-reported questionnaire, was used in two languages, English and Malay. Both language version of SF-36 used in this study was translated and validated in the Malaysian population. This questionnaire covers eight domains/subscales of quality of life, comprising of physical facet (physical health components) and psychosocial facet (mental health components) of quality of life. The physical health consisted of Physical Functioning, Physical Role, Bodily Pain and General Health perception, while the mental health components are Role Emotional, Vitality, Mental Health and Social Functioning.

Patients were assigned randomly to two separate groups using a sealed envelope with treatment allocation inside; HBOT group and control group. Treatment in both groups included mechanical/chemical debridement, antibiotics, wound dressing and off-loading footwear. Only the HBOT group were subjected for hyperbaric oxygen therapy. Each session was conducted five days a week in mono-place hyperbaric chamber. (20-30 treatment sessions). A session consisted of a duration of compression

in air for 5 mins, subsequently at 2.5 atmosphere absolute (ATA) treatment period for 85 mins, and then a 5 mins decompression period.

DATA ANALYSIS

SPSS version 22.0 software was used to analysed the data collected. Descriptive and analytical statistical functions of the software was used to analysed the demographic and clinical characteristics of the study sample. Independent t-test using a two-tailed test was used to compare mean values of continuous data and χ^2 test was used to compare categorical data in order to evaluate inter-group differences. Mann Whitney-U test was used to compare the median score for each SF-36 domain and the summary scores between the two groups as the data was not normally distributed.

RESULTS

DEMOGRAPHIC DATA

A total of 60 patients were recruited and analysed in present study and they were randomly divided into two groups. These patients were aged between 39 to 77 years in which 31 were males (51.2%) and 29 (48.3%) were females. A total of 14 (23.3%) of them were active smokers while another 46 (76.7%) were non-smokers, or had quit smoking more than 20 years. A total of 25 (41.7%) had chronic medical problem (chronic kidney disease, retinopathy, ischaemic heart disease). Mean duration of the

Table 1: Demographic data of the respondents

Variables	HBOT group (n=30)	Control group (n=30)	p Value
Age in years (Mean ± s.d.)	54.23 ± 10.20	58.70 ± 11.30	0.081
Gender			
Male	11 (36.70%)	20 (66.70%)	
Female	19 (63.70%)	10 (33.30%)	
Wagner Classification			
Type 1	5 (8.33%)	4(6.67%)	
Type 2	13 (21.67%)	13 (21.67%)	
Type 3	12 (20.00%)	13 (21.67%)	

chronic diabetic foot ulcer was 5.2 months, with 9 (16.7%) were type 1, 26 (43.3%) were type 2 and 25 (41.7%) were type 3 ulcers based on Wagner classification system (Table 1).

ANALYSING TOTAL WHITE CELL COUNT (TWCC) CHANGES IN HBOT AND CONTROL GROUP

During initial presentation, the total white cell count (TWCC) was high in both groups, but there was no significant different statistically at the initial presentation (p=0.087). The reduction of WCC was seen in both groups. However, the trend was more steady in the HBOT group until the end of treatment at day-30, and mostly had normalise. The reduction was significant in HBOT group (p=0.046) (Figure 1).

ANALYSING C-REACTIVE PROTEIN (CRP) CHANGES IN HBOT AND CONTROL GROUP

Similar to the TWCC changes, both groups have high C-reactive protein (CRP) at the initial presentation.

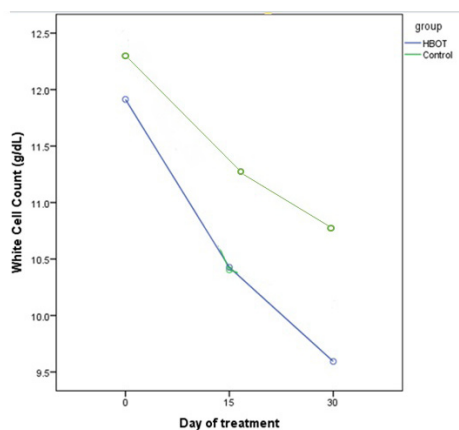


Figure 1: White cell count reduction throughout

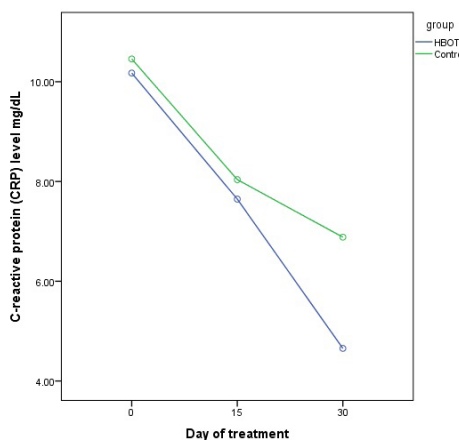


Figure 2: C-reactive protein (CRP) level reduction throughout treatment



Figure 3: Photo showing ulcer size reduction after one month of HBOT

Table 2: Ulcer reduction with treatment

Day of treatment	HBOT (in cm ²)	Control (in cm ²)	p-Value
D0	10.5 (7.0-14.1)	12.8 (9.2-16.3)	0.060
D10	6.8 (3.6-9.9)	12.1 (8.9-15.2)	<0.001
D20	5.1 (2.0-8.1)	11.6 (8.6-15.2)	<0.001
D30	3.6 (0.7-6.4)	10.7 (7.8-13.6)	<0.001

Independent t-test (*significant if p<0.05)

Reduction of CRP protein was observed throughout the treatment in HBOT and the control group. The reduction trend was significant statistically in HBOT group which was more constant and steady compared to the control group (p=0.039) (Figure 2).

ANALYZING ULCER REDUCTION IN HBOT AND CONTROL GROUP

During the initial presentation, the ulcer size was statistically not significant in both groups (p=0.06). With the treatment, reduction in size of the ulcer was observed in both groups, and it was significant (p<0.001) in HBOT group (Figure 3). Using Pairwise comparison, wound reduction in

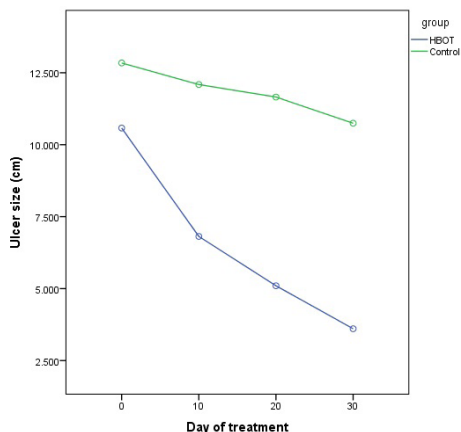


Figure 4: Ulcer size reduction throughout treatment

every ten days of measurement was significant (p<0.001) in HBOT group compared to the control group (Table 2, Figure 4).

Table 3: The scores of eight SF-36 domains and two summary components

SF-36 domains and summary scales	HBOT group (n=30)	Control group (n=30)	p-Value (Mann-Whitney U test)
Physical Functioning	60.0	46.7	<0.001
Role Physical	49.0	42.5	0.042
Bodily Pain	59.0	80.9	<0.001
General Health	56.0	38.3	<0.001
Vitality	67.5	49.0	0.005
Social Functioning	50.0	30.0	0.029
Role Emotional	66.7	40.7	<0.001
Mental Health	70.4	51.2	0.028
Physical Component Summary	55.8	50.0	0.001
Mental Health Summary	65.3	53.8	0.001

(Values are expressed as median (25th-75th percentiles) with 0 as poorest health and 100 as the best health)

*significant if $p < 0.05$

ANALYSING THE QUALITY OF LIFE USING SF-36

There was statistically significant difference in both group of each domain. Patients treated with HBOT have better physical and mental health. Table 3 shows eight domain median scores and the SF-36 two summary scales. Mostly, diabetic foot ulcer treated without HBOT had lower median scores in all of SF-36 domains significantly. Hence, diabetic foot ulcer treated with HBOT had better quality of life. The summary scores showed a significantly poor Physical Component Summary in patients underwent HBOT than those treated with conventional treatment alone. This was also seen in Mental Component Summary with p value equal to 0.001.

DISCUSSION

The present study supports the management approach that use HBOT as an adjunct to the usual

DFU treatment for selected diabetic patients as it enhances the healing of ulcers. HBOT had accelerated ulcer healing patients suffering from long-standing chronic ulcers compared to the control group treated with conventional treatment alone. All sixty patients (thirty in each group) in present study were compliant to each follow up and assessments. We found no significant difference in patients who were smoking ($p = 0.06$) or who had chronic medical illnesses such as chronic kidney disease, ischaemic heart disease, diabetic retinopathy etc. ($p = 0.087$), in both groups of HBOT and control group.

Patients having chronic diabetic foot ulcers were susceptible to develop recurrent infections, particularly when the wound failed to heal. In previous study, these patients needed multiple surgical debridement, antibiotic courses and prolong hospital stay. To monitor infections in our study, we used reliable infective markers such as white cell count and C-reactive protein

level (Lipsky et al. 2012). The reduction of the infective markers (WCC and CRP) were seen in both group, which were statistically significant ($p=0.046$ and 0.039 , respectively). We noticed that patients in both group developed not only recurrent infections due to the foot ulcers, but also from other sources (e.g. respiratory, urinary tract infections) thus exacerbating and influences the level of infective markers. Patients who developed infection in this study, with evidence of clinical and biochemical findings were treated accordingly.

This explains the steady reduction trend of white cell count and C-reactive protein in the HBOT group, as the elevation of oxygen tension enhances the neutrophil oxidative killing of bacteria in addition to oxygen being directly toxic to anaerobic organisms. Previous studies supports the use of HBOT in the treatment of chronic diabetic foot ulcers which significantly improve wound healing (Barnes 2006; Londahl et al. 2010; Lipsky & Berendt 2010). We noticed similar outcome in this study and it is remarkably significant where the wound reduction seen in every phases of assessment which was conducted in every ten days of the treatment. Using pairwise comparison, the p value in each phase was less than 0.001 compared to the control group treated with conventional therapy alone. At six months follow up, 26 patients (86.7%) in HBOT group achieve complete ulcer healing as compared to 18 patients (60%) in the control group.

Diabetic complications may greatly interfere with the quality of life of diabetic patients (Wandell & Tovi

2000). The effect of foot problems to the QOL is the most popularly studied using self-reported SF-36 questionnaire. There were significantly different scores of all domains and the two summary scales in the SF-36 two groups. The Physical Functioning domain governs all physical tasks such as bending, stretching, walking and climbing stairs without limitation while the Role Physical domain tests on predicaments of tasks or other daily activities resulting from the physical health. The control group scored significantly, indicating severe and relentless restrictions with mobility. This is probably due to inability to mobilize secondary to non-weight-bearing regimen from foot ulcer. Mental health was not as severely impaired as some of the components in physical health. Our findings are in agreement of several studies that also focus on quality of living among patients struggling Diabetic Foot Ulcer. Such studies are by Valensi et al. (2005) and Ribu et al. (2006), of which both studies use the SF-36 Questionnaires and these two studies were both cross-sectional and observational design, only that Ribu et al. (2006) compared the scores of patients with DFU ulcer score to the general population without Diabetes where as Valensi et al. (2005) compared the QOL among Diabetic patients with and without DFU. These studies however, did not measure HBOT influence on ulcer healing and quality of living. Another study with results consistent to present study was done by Mazlina et al. (2011) and it compared the health-related quality of life in patients with DFU to diabetic

patients without DFU, using the SF-36 questionnaires, it was observed that the two domains of physical health such as physical functioning and role physical domain were affected negatively great in patients with DFU. They also observed that mental health was affected but not as severely as the physical component.

Mental health measures the level of happiness, general well-being and constraints that emotional issue drawback on the degree of task one is able to carry out. The probable cause for patients in the control group having significantly low mental health score was attributed to having doubts as to when or whether the foot problems will heal. They may experience poorer psychosocial adjustments and experience living constraints.

Admittedly, the sample size for the present study was small due to this is pilot study in the country. It aims to study the effects of DFU towards quality of life but also the outcome of HBOT. Therefore, a bigger sample size is recommended for future study. We also had limitation to control each single dressing to be used in both HBOT and control groups.

CONCLUSION

In conclusion, it must be emphasised that HBOT is an adjunctive therapy to many other components essential in accelerating wound healing and in achieving better quality of life in chronic non-healing diabetic foot ulcer. The results of present and precedent should provide impetus and basis for larger multicentre prospective, randomized,

double-blinded controlled studies in assessing the outcome of HBOT in healing of diabetic foot ulcers.

ACKNOWLEDGEMENT

The authors would like to thank Professor Dr Srijit Das for his technical help in publishing this manuscript. The authors would also like to thank Mr Mohd Amir Azmi for his help in ensuring high quality pictures.

REFERENCES

- Almzaiel, A.J., Billington, R., Smerdon, G., Moody, A.J. 2013. Effects of hyperbaric oxygen treatment on antimicrobial function and apoptosis of differentiated HL-60 (neutrophil-like) cells. *Life Sci* 93(2-3): 125-31.
- Barnes, R.C. 2006. Point: hyperbaric oxygen is beneficial for diabetic foot wounds. *Clin Infect Dis* 43(2): 188-92.
- Eggleton, P., Bishop, A.J., Smerdon, G.R. 2015. Safety and efficacy of hyperbaric oxygen therapy in chronic wound management: current evidence. *Chronic Wound Care Management and Research* 2: 81-93.
- Fejfarová, V., Jirkovská, A., Dragomirecká, E., Game, F., Bém, R., Dubsk, M., Wosková, V., K í ová, M., Skibová, J., Wu, S. 2014. Does the diabetic foot have a significant impact on selected psychological or social characteristics of patients with diabetes mellitus? *J Diabetes Res* 2014: 371938.
- Goodridge, D., Trepman, E., Embil, J.M. 2005. Health-related quality of life in diabetic patients with foot ulcers: literature review. *J Wound Ostomy Continence Nurs* 32(6): 368-77.
- Herber, O.R., Schnepf, W., Rieger, M.A. 2007. A systematic review on the impact of leg ulceration on patients' quality of life. *Health Qual Life Outcomes* 5: 44.
- Kendall, A.C., Whatmore, J.L., Winyard, P.G., Smerdon, G.R., Eggleton, P. 2013. Hyperbaric oxygen treatment reduces neutrophil-endothelial adhesion in chronic wound conditions through S-nitrosation. *Wound Repair Regen* 21(6): 860-8.
- Kinmond, K., McGee, P., Gough, S., Ashford, R. 2003. 'Loss of self': a psychosocial study of the quality of life of adults with diabetic foot ulceration. *J Tissue Viability* 13(1): 6-8.

- Kranke, P., Bennett, M., Roeckl-Wiedmann, I., Debus, S. 2004. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* (2): CD004123.
- Lipsky, B.A, Berendt, A.R. 2010. Hyperbaric oxygen therapy for diabetic foot wounds: has hope hurdled hype? *Diabetes Care* 33(5): 1143-5.
- Lipsky, B.A., Berendt, A.R., Cornia, P.B., Pile, J.C., Peters, E.J., Armstrong, D.G., Deery, H.G., Embil, J.M., Joseph, W.S., Karchmer, A.W., Pinzur, M.S., Senneville, E. 2012. 2012 Infectious Disease Society of America clinical practice guidelines for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 54(12): e132-e173.
- Londahl, M., Katzman, P., Nilsson, A., Hammarlund, C. 2010. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 33(5): 998–1003.
- Mazlina, M., Shamsul, A.S., Jeffery, F.A. 2011. Health-related quality of life in patients with diabetic foot problems in Malaysia. *Med J Malaysia* 66(3): 234-8.
- Ribu, L., Rustoen, T., Birkeland, K., Hanestad, B.R., Paul, S.M., Miaskowski, C. 2006. The prevalence and occurrence of diabetic foot ulcer pain and its impact on health-related quality of life. *J Pain* 7(4): 290-9.
- Ribu, L., Wahl, A. 2004. Living with diabetic foot ulcers: a life of fear, restrictions, and pain. *Ostomy Wound Manage* 50(2): 57-67.
- Valensi, P., Girod, I., Baron, F., Moreau-Defarges, T., Guillon, P. 2005. Quality of life and clinical correlations in patients with diabetic foot ulcers. *Diabetes Metab* 31(3 Pt 1): 263-71.
- Wandell, P.E., Tovi, J. 2000. The quality of life of elderly diabetic patients. *J Diabetes Complications* 14(1): 25-30.

Received: 13 January 2017

Accepted: 2 June 2017