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Original Article

By-products of lithotripsy: Are they related to abdominal fat and wave characteristics?

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الملخص

أهداف البحث: تهدف هذه الدراسة إلى تقييم العلاقة بين المنتجات الجانبية لموجات تفتيت الحصوات الصدمية خارج الجسم وبعض العوامل الفيزيائية مثل الدهون في منطقة البطن، مستويات الطاقة ونبضات موجة الصدمة.

طرق البحث: استهدفت الدراسة ٤٠ مريضا (٢٠ ذكرا، و٢٠ أنثى) أعمارهم ٣٧.١٨ ± ١٠.٦٤ لديهم حصوات في الكلية أو الحالب. تم علاج جميع المرضى بموجات تفتيت الحصوات الصدمية خارج الجسم وتم قياس الدهون في منطقة البطن بواسطة جهاز أمرون لقياس دهون الجسم وتم حساب مؤشر كتلة الجسم. كما تم قياس المعاملات مثل علامات الإجهاد التأكسدي، والكيتونات، والبروتين في عينات البول قبل وبعد موجات تفتيت الحصوات الصدمية خارج الجسم. وتم تحديد خصائص موجات التفتيت ونبض الموجة.

النتائج: أظهرت النتائج ارتفاعا إحصائيا ملحوظا في مستويات كل من علامات الإجهاد التأكسدي والكيتونات في البول بعد التعرض لموجات تفتيت الحصوات الصدمية خارج الجسم مقارنة بقيمها ما قبل التعرض لموجات تفتيت الحصوات الصدمية خارج الجسم. أظهرت النتائج ارتفاعا ملحوظا في علامات الإجهاد التأكسدي والكيتونات عند كلا من المرضى الذكور والإناث. بالإضافة إلى ذلك، كان هناك علاقة ملحوظة بين علامات الإجهاد التأكسدي والكيتونات مع مستويات الطاقة إضافة إلى وجود ارتباط كبير بين الكيتونات ومؤشر كتلة الجسم عند المرضى الإناث. كشف التحليل أيضا أن نبض موجة الصدمة كان له تأثير ضئيل على معامل المنتجات الجانبية.

الاستنتاجات: ينصح المرضى الذين يعانون من زيادة الوزن والبدانة بالتعرض لمستوى الطاقة ≤ ٤ جول. بالإضافة إلى ذلك، ينبغي النظر بعد موجات تفتيت الحصوات الصدمية خارج الجسم لمستوى علامات الإجهاد التأكسدي البولية كاختبار روتيني خاصة عند الذكور البدناء.

الكلمات المفتاحية: الدهون في منطقة البطن؛ الكيتونات؛ علامات الإجهاد التأكسدي؛ البدانة؛ موجات تفتيت الحصى الصدمية

Abstract

Objectives: This study aimed to evaluate the correlations between by-products of extracorporeal shock wave lithotripsy (ESWL) and some physical parameters such as abdominal fat, energy levels, and shock wave pulses.

Methods: A total of 40 patients (20 men and 20 women), aged 37.18 ± 10.64 years, with renal or ureteral stones were recruited. All patients were treated with ESWL, and their abdominal fat was measured using an Omron body fat monitor and the body mass index (BMI). Parameters such as the levels of malondialdehyde (MDA), ketones, and protein in urine were measured before and after ESWL using a Bio Doctor Analyzer. The wave characteristics of the lithotripsy procedure and the wave pulses were determined.

Results: The mean levels of urinary MDA and ketones showed statistically significant increases in post-ESWL compared with pre-ESWL values. The results showed significant elevations in MDA and ketones in both male and female patients. In addition, there was a significant correlation between MDA/ketones and energy levels and between ketones and BMI in female patients. The analysis also revealed that the shock wave pulse had an insignificant impact on the by-product parameters.

Conclusion: An energy level of ≤4 J is recommended for overweight and obese patients undergoing ESWL. In addition, measurement of the post-ESWL MDA urinary level should be performed as a routine test, especially in obese male patients.

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Keywords: Abdominal fat; Ketones; Malondialdehyde; Obesity; Shock wave lithotripsy

Introduction

Extracorporeal shock wave lithotripsy (ESWL) is considered the first-line treatment, and has become the standard therapy, for most patients with renal and ureteric calculi because it is a convenient, safe, and non-invasive outpatient procedure, with success rates of 60–99%.[1–3]

To optimize the results of ESWL, several technical factors should be considered. Some of these factors are related to the patients themselves, whereas the others are related to the stone, such as stone size and density, skin-to-stone distance (SSD), and specific location of the stone, which help predict the chances of treatment success.[4,5] The type of lithotripters and the way they work may also influence the results of ESWL. However, obesity metrics such as body mass index (BMI) and SSD have been evaluated as predictors of ESWL success, and SSD has specifically demonstrated a strong correlation with the success rate.[6–9] Furthermore, Mezentsev and Juan et al. have confirmed the correlation between the ESWL outcomes and BMI in their studies.[7,10] These studies showed that higher quantities of fat, especially abdominal fat (AF), are associated with a lower calculus-free rate after ESWL treatment.[10,11] The influence of BMI on the complete clearance of renal stones remains indistinct. Regardless of whether BMI affects the results or not, it could be considered as one major reason for the formation of by-products of ESWL treatment.[12] Despite the advantages of ESWL, a few serious adverse effects could emerge. The most common of these adverse effects are tissue damage (bleeding and oedema) and cavitation.[13] The potential danger of cavitation is not only of a physical nature but also of a chemical nature because of the generation of free radicals (e.g. OH, .H, and O_2).[14,15] ESWL is believed to induce free radical activity, thus giving rise to oxygen free radical compounds,[16] which are considered more dangerous than bleeding and oedema because of their hidden nature.

This study aimed to assess the impact of physical parameters such as BMI (AF), energy level (EL), and number of shock wave pulses (SWPs) on ESWL by-products, particularly oxidative free radicals that can be estimated from malondialdehyde (MDA) as a biomarker. In addition, other by-products induced by ESWL, such as ketones and protein, were also studied. All these by-products of ESWL were analysed regardless of the stone-free rate.

Materials and Methods

A hospital-based cross-sectional study was conducted on 40 patients aged 37.18 ± 10.64 years, with renal or ureteral stones from 7 to 15 mm in size, from the outpatient department of the lithotripsy unit of a local private hospital from January to April 2016. The patients comprised 20 men (50%) and 20 women (50%). The stone localization (e.g. pelvis, calyx, and ureter) was determined but the size was not specified.

Anthropometric assessments included measurement of height to the nearest 0.1 cm by using a graduated elastic tape, and measurement of body weight to the nearest 0.1 kg with the patient in light clothing and without shoes, by using the Omron Body Composition and Body Fat Monitor (BF508; Omron Healthcare Co., Ltd., Japan). This standard digital scale was also used to measure the visceral AF. BMI was calculated as the weight (kg) divided by the square of height (m^2) and classified according to World Health Organization (WHO) criteria. The patients were classified according to their body weight as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese class I (30–34.5 kg/m^2), and obese class II (35–40 kg/m^2), on the basis of the values provided by the WHO. The patients were also classified according to their AF as underweight (<4 kg), normal (>4 kg), pre-obese (10 kg), obese class I (13.5 kg), and obese class II (17 kg), based on the high positive correlation between BMI and AF. All patients were exposed to a Siemens Electromagnetic Modularis Lithotripter (C-plus; Siemens Healthcare GmbH, Germany) that has been installed since 2012 at the private hospital where the study was conducted. The EL was between 0.1 and 8 J (adjustable in 38 steps), and the penetration depth was up to 140 mm at the focus centre. The patients met all the necessary prerequisites before the ESWL treatment. The number of shock waves per session ranged from 1700 to 3000 pulses (average pulse rate, 120/min). The average pulse usually depends on the patient's parameters (e.g. body weight, waist thickness). The exposure time ranged from 25 to 45 min without the need for anaesthesia. Urine samples were collected before and after the ESWL sessions and were analysed for by-products by using Bio Doctor Analyzer (BS502; Bionics Co., Ltd, Korea). The expected time for sample collection was dependent on the time of the treatment session. The by-product parameters included MDA, ketone, and protein levels in urine.

The Statistical Package for Social Sciences (SPSS) was used for data analysis. Data were presented as mean values and standard deviations for different exposure conditions pre- and post-ESWL. Fold rates were calculated as the ratio between post- and pre-ESWL values. The differences in fold rates were tested for significance with the two-sample t-test. The level of statistical significance was set as $P \leq 0.05$. The correlations of BMI, EL, and SWP with urine test parameters were assessed using box plots.

As the study was conducted on humans, the Ethical Principles for Medical Research Involving Human Subjects had been taken into account. Ethical approval was provided by the General Directorate of Health-Duhok in January 2016. Moreover, consent from patients was obtained in advance. Finally, the patients' consent was obtained before beginning the research, and they were informed that their data will be used exclusively for this study.

Results

Table 1 shows the mean ± standard deviation values of the anthropometric measurements of the patients. Male

Table 1: Patients' anthropometric data, body fat characteristics, and shock wave properties.

Parameters	Total (N = 40) Mean ± SD	Male patients (n = 20) Mean ± SD	Female patients (n = 20) Mean ± SD	P-value
Age (years)	37.18 ± 10.64	33.25 ± 6.51	41.1 ± 12.54	<0.05[a]
Height (cm)	165.03 ± 8.24	171.61 ± 5.108	158.45 ± 4.696	<0.05[a]
Weight (kg)	77.52 ± 14.39	83.4 ± 14.78	71.65 ± 11.56	<0.05[a]
BMI (kg/m^2)	28.06 ± 4.37	28.48 ± 4.71	28.55 ± 4.28	NS
Abdominal fat (kg)	10.07 ± 0.69	11.4 ± 4.25	9 ± 3.31	<0.05[a]
Energy level (J)	3.78 ± 0.67	3.89 ± 0.72	3.66 ± 0.62	NS
Shock wave pulses (pulses/min)	2229 ± 430	2091 ± 470	2375 ± 342	NS

Values are presented as means ± standard deviations.
SD, standard deviation; BMI, body mass index.
[a] t-test, correlation is significant at the P < 0.05 level. NS, non-significant.

Table 2: Statistical analysis of urinary measurement data pre- and post-ESWL.

Parameters	Pre-ESWL Mean ± SD	Post-ESWL Mean ± SD	P-value
MDA (μmol/L)	5414.1 ± 1896.8	9096.7 ± 2587.2	<0.05[a]
Ketones (mg/dL)	10.73 ± 23.58	28.1 ± 32.74	<0.05[a]
Protein (mg/L)	37.45 ± 17.51	45.78 ± 41.83	NS

Values are presented as means ± standard deviations.
ESWL, extracorporeal shock wave lithotripsy; SD, standard deviation; MDA, malondialdehyde.
[a] t-test, correlation is significant at the p < 0.05 level, NS non-significant.

patients were younger, taller, heavier, had more AF, and had slightly lower average BMI than female patients. In male patients, all BMI categories were represented. However, none of the female patients fell into the underweight (<18.5 kg/m^2) BMI category. This indicates that the percentages of overweight and obesity were higher in female patients than in male patients.

Table 2 shows the results of urine analysis before and after ESWL treatment for all patients. The pre- and post-ESWL values for each parameter of the urine test were compared using a paired t-test. The comparison showed no statistical difference in terms of protein levels. In contrast, significant (P < 0.001) differences in MDA and ketone levels were found between pre- and post-ESWL treatment in both male and female patients. These results are shown in Figures 1 and 2.

To assess the impact of the physical parameters (BMI, EL, and SWP) on MDA and ketone levels, the correlation and analysis of the combined experimental data of MDA and ketones in urine were assessed under the influence of each of BMI (AF), number of SWPs, and EL.

In male patients, the MDA fold rates were not correlated with BMI (AF) at an average EL of <4 J but were significantly (P < 0.05) correlated with EL at an average BMI of >27 kg/m^2, as shown in Figure 3A. In female patients, the MDA fold rates were almost positively correlated with the EL (2.85, 3.5, and 4 J) at an average BMI of 27 kg/m^2, as shown in Figure 3B, although it was not statistically significant.

Concerning ketone bodies, a noticeable increase in the ketone fold rates in urine samples was found. This increase in ketones was attributed to increased fatty acid metabolism by the liver after shock wave treatment. This was found in patients of both sexes (P < 0.05), as previously illustrated in Figure 2.

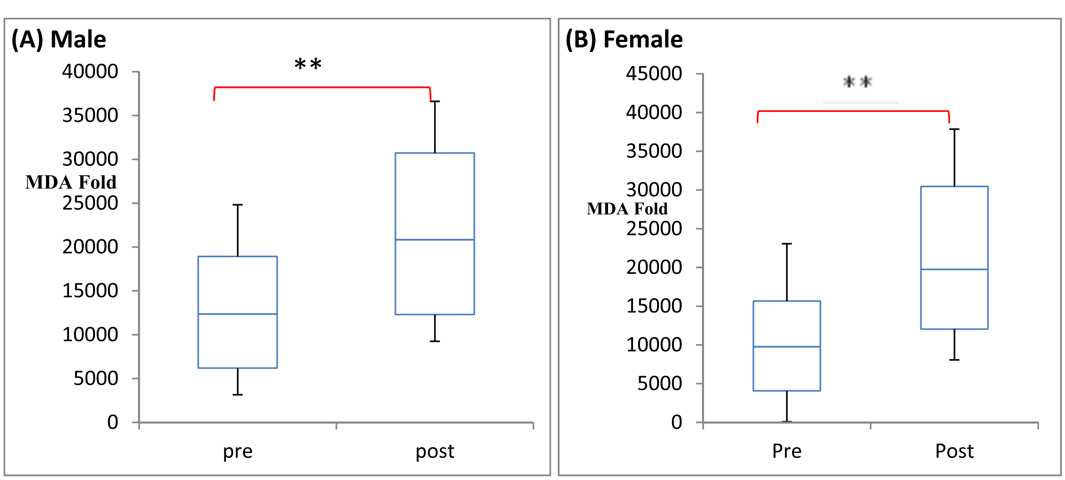

Figure 1: Malondialdehyde (MDA) fold before (Pre) and after (Post) extracorporeal shock wave lithotripsy treatment in (A) male and (B) female patients.

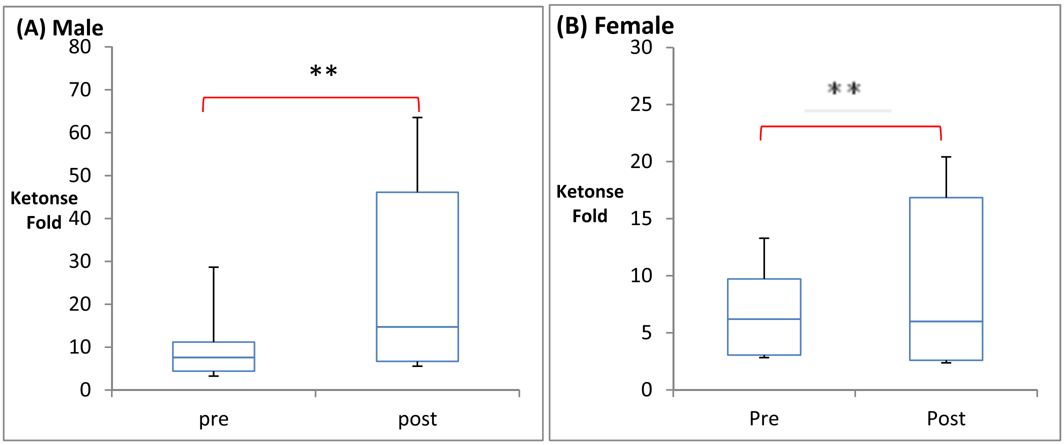

Figure 2: Ketone fold rates before (Pre) and after (Post) extracorporeal shock wave lithotripsy treatment in (A) male and (B) female patients.

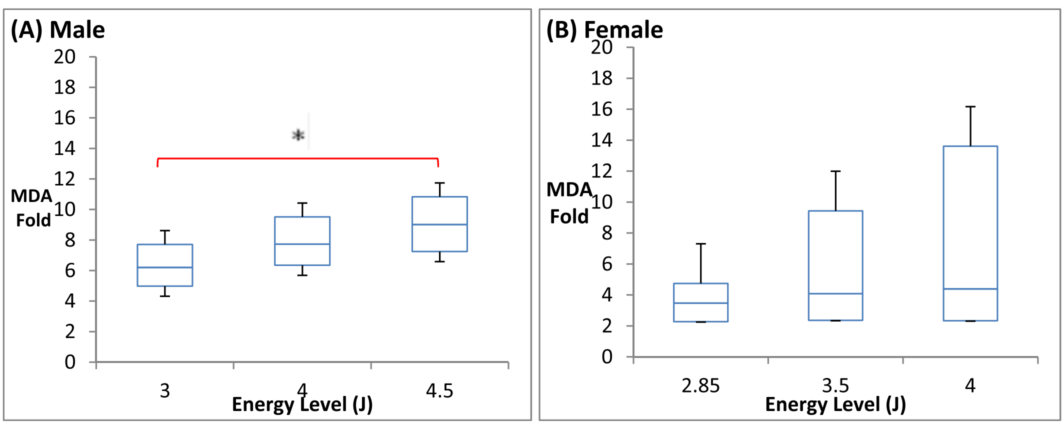

Figure 3: Malondialdehyde (MDA) fold rate as a function of energy level in (A) male and (B) female patients.

In female patients, the ketone fold rates showed a significant difference ($P < 0.05$) with respect to BMI at an average EL of <3.5 J. However, these rates did not show a significant difference with respect to EL at an average BMI of >27 kg/m^2, as shown in Figures 4B and 5B. In contrast, in male patients, the ketone fold rates demonstrated a significant difference with respect to EL, particularly at higher ELs, whereas these rates were not significant with respect to BMI, as shown in Figures 4A and 5A. However, SWP did not show a noticeable correlation with MDA or ketones.

Figure 6(A and B) shows the relationship of ketone fold rates with EL in male patients and with BMI in female

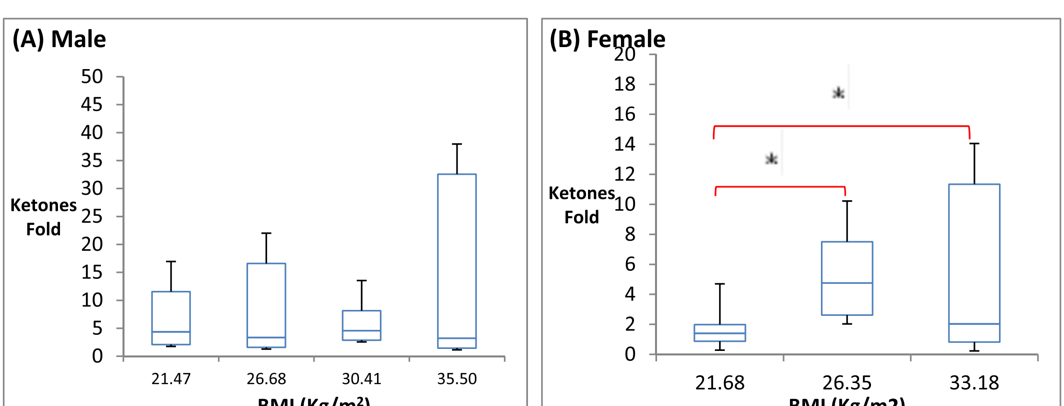

Figure 4: Correlation of ketone fold rates with body mass index (BMI, abdominal fat) in (A) male and (B) female patients.

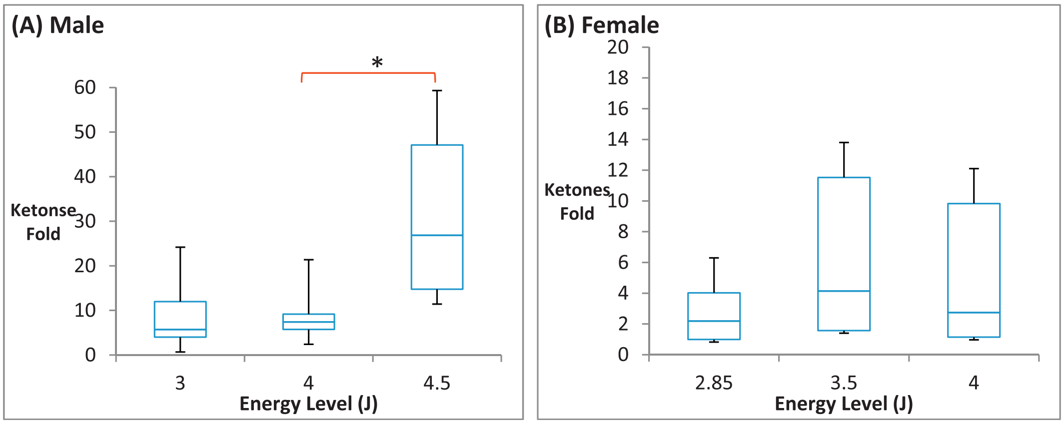

Figure 5: Ketone fold rate as a function of energy level in (A) male and (B) female patients.

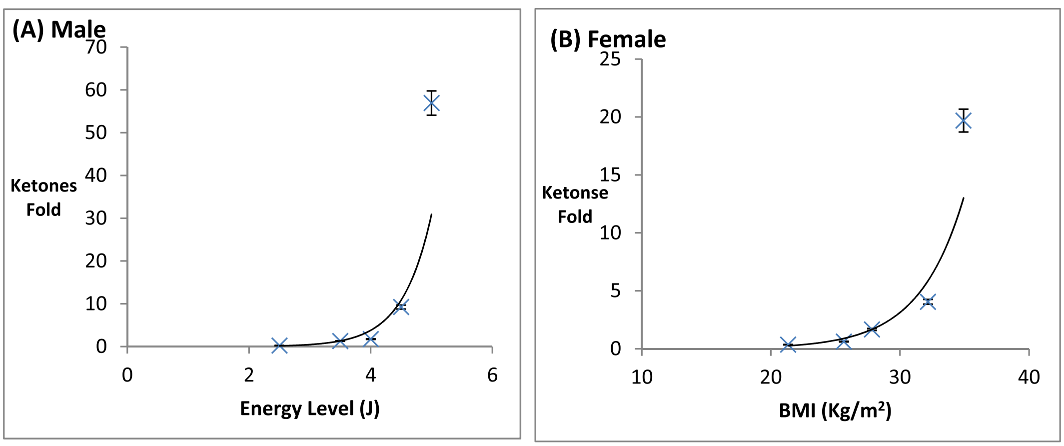

Figure 6: Ketone fold rates increase exponentially with energy level in male patients (A) and with body mass index (BMI) in female patients (B).

patients. The data were fitted using exponential regression for ketone fold rates. The best-fit equation approximates are shown in equations (1) and (2):

$$\textbf{Ketone fold} = 0.0009\ \textbf{exp}^{2.1\ \textbf{EL}} \quad (1)$$

$$\textbf{Ketone fold} = 0.0005\ \textbf{exp}^{0.3\ \textbf{BMI}} \quad (2)$$

The coefficients of determination (R^2) were 0.94 and 0.95 for equations (1) and (2), respectively. These equations reveal that the impact of EL on the ketone fold rates in male patients was more pronounced than the impact of BMI in female patients.

Figure 6(A and B) reveals that the cut-off value of EL in male patients was >4 J, which is rather high, and the cut-off value of BMI (AF) was >27 kg/m^2, which represent the range of overweight. These cut-off values are also shown in Figures 4B and 5A.

Discussion

The present study addressed the impact of BMI in terms of AF on the by-products of ESWL, particularly with respect to oxidative free radical (estimated from MDA as a biomarker) and ketone formation. The results showed that the mean levels of urinary MDA and ketones statistically significantly increased after ESWL treatment. These results were in total agreement with those of previous studies that assessed MDA levels after ESWL.[17,18] The elevation in MDA levels could be explained by the mechanism of oxidation product formation. Free radical formation after ESWL treatment has been reported in previous studies.[19,20] As a result of ESWL, lipid peroxides and oxidation products are generated and the MDA level is increased. Despite the direct effects of the number of pulses of ESWL on oxidative stress identified by a previous study,[21] our results showed that this proportionality is almost null for both normal and overweight patients.

Most of the previous studies analysed MDA level as a function of time after ESWL treatment.[17,18] Notably, none of them assessed the impact of AF on the MDA level while taking into account the differences in EL and number of shock waves. In contrast, this study was conducted to show the impact of BMI (AF), EL, and SWP on the MDA level in urine after ESWL, as a potential adverse effect of treatment. The MDA fold rates were significantly increased ($P < 0.05$) post ESWL in male patients who were administered an EL of >4 J. In this study, the correlation between MDA and EL is more pronounced in male patients than in female patients. This evidence suggests that increased MDA formation induced by ESWL is an energy-dependent matter. Furthermore, the outcome of this study confirmed the limited impact of BMI on MDA formation at an EL of <4 J, and reinforces the importance of EL on the by-products of ESWL, especially in overweight and obese male patients.

Despite the lack of genuine connection between ketones and ESWL, a significant increase ($P < 0.05$) could be seen in the ketone fold rates after treatment in terms of both BMI and EL. Basically, the high level of ketones (higher than normal values ≤1 mg/dL) could be attributed to the long fasting period of the patients (about 24 h). This fasting period is required before ESWL sessions. In normal cases, ketones will be completely metabolized, such that low ketone levels will be detected in urine. However, when the body lacks glucose for energy, it will consume the body fats, resulting in increased production of ketones (detectable in blood and urine). This may lead to an elevation in the ketone level before ESWL. In contrast, ESWL may be responsible for the high fold rates of ketones after treatment, as a result of the alteration in intra-renal metabolism[22] that occurs to repair the tissues damaged by high ESWL energies. The ultrasound wave produces a thermal effect that increases the local metabolism. In addition, the attenuation coefficient of fat produces excess heat from high-energy ultrasound deposition, as reported by Pragya and Srivastava.[23] This, in turn, will activate the metabolism of AF and produce high ketone levels. Generally, heat is generated whenever ultrasound energy is absorbed, and the amount of heat produced depends on the intensity of the ultrasound, the time of exposure, and the specific absorption characteristics of the tissue.[24] Moreover, the highest rate of ultrasound attenuation occurs in fatty tissues.[25] On the other hand, the attenuation in ultrasound decreases linearly when BMI is increased independent of the patient's sex.[26] Accordingly, the ketone fold rates increased in female patients (although they were administered low EL), most of whom had a high BMI. The elevation in ketone fold rates as a function of EL in overweight male patients could be explained by the hypothesis concerning the induction of sonoporation by ultrasound in adipocytes, which leads to the release of lipid content into microcirculation.[27]

Conclusions

Although ESWL has the same success rate in fragmenting stones regardless of whether the waves pass through fatty or non-fatty tissues, the procedure is often accompanied by the formation and increased urinary levels of some by-products such as MDA (an oxidative stress biomarker) and ketones. Elevations of MDA and ketone levels were more evident in overweight and obese male patients in terms of high ELs. Accordingly, this may require the evaluation of the patient's fat percentage to adjust the suitable EL. In contrast, the elevation of ketone levels was more noticeable in female patients in terms of BMI (AF) even at an EL less than the cut-off value (<4 J). For patients of both sexes, the by-product parameters did not show any significant correlations with the number of SWPs.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This study was undertaken on human beings so that, all Ethical Principles for Medical Research Involving Human Subjects took into account. The information in this study was used only for research purposes. Ethical approval was obtained by the Directorate General of Health - Duhok in January 2016. Patients consent was also obtained in advance.

Recommendations

Patients who are overweight and obese should not be exposed to an EL of >4 J. Moreover, it is recommended that an MDA test be performed as a routine assessment after ESWL, especially in obese male patients.

Authors' contributions

RAN and HA proposed the idea, designed the study, interpreted data and wrote initial and final drafts. BS collected, organized and analyzed data, in addition to literature search. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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