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Genetic Risk Factors

Histopathology, Radiography

Highlights

Tomography for Diagnoses

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Discovering Thoughts, Inventing Future

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Genetic Risk Factors, Biology, Psychosocial Aspects, and Comparison between Male Breast Cancer and Female Breast Cancer

By Mojgan Haji Seyed Ebrahim Darkeh & Edward Azavedo
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GENETICRISKFACTORSBIOLOGYPSYCHOSOCIALASPECTSANDCOMPARISONBETWEENMALEBREASTCANCERANDFEMALEBREASTCANCER

Strictly as per the compliance and regulations of:

Genetic Risk Factors, Biology, Psychosocial Aspects, and Comparison between Male Breast Cancer and Female Breast Cancer

Mojgan Haji Seyed Ebrahim Darkeh [α] & Edward Azavedo [σ]

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Conclusion: Increased input is needed for informative and psychological support for MBC patients. Public education should be oriented. Toward men at higher risk to reduce symptom duration before diagnosis.

I. Introduction

Male breast cancer is a relatively rare disease, which accounts for less than 1% of all instances of cancer in men and about 1% of all breast cancer cases (1- 7). It accounts for less than 0.2% of all cancer related deaths among men (8- 11). Because of the rarity of the disease, most information about male breast cancer has been obtained from small, mono-centric, retrospective studies or through extrapolation from randomized prospective studies or from clinical experience of breast cancer in women (12). But this enormous volume of data on female breast cancer may not be completely relevant to men, particularly with regard to differences concerning the hormonal environment for men and women, and also in terms of gender differences that may affect the cancer patient's condition, medical and/or psychosocial side effects from treatments, and survival priorities.

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II. Method

This study is a systematic review of the literature. The literature review was conducted in order to describe the current state of knowledge and to compile the scientific literature within the field of breast cancer in men. The study processes the scientific papers in a systematic manner, which consisted of both empirical studies of quantitative and qualitative design, and theoretical or meta-analytic and overview studies. All of them had a clear link to breast cancer in men. The search for scientific literature was conducted in the PubMed database by searching for the key words "male breast cancer" and some articles were also selected from bibliographies from other publications.

Articles that were included in this study meet these criteria

- Articles in English language published between 1990-01-01 and 2013-09-30.
- Articles were about primary breast cancer in men.
- Articles touched heredity and genetic aspects, clinical features, clinical histopathology, diagnosis and diagnostic methods (mammography, ultrasound, fine needle aspiration biopsy / core needle biopsy and sentinel lymph node biopsy), treatment (surgery, radiotherapy, hormone therapy and chemotherapy), prognosis (prognostic factors and survival), and psychosocial aspects.
- Articles made a clear comparison of breast cancer in men and breast cancer in women

Articles were excluded if one or more of the following criteria were matched

- Articles that were case studies or studies with less than 10 patients (with the exception of case studies of unknown / rare genetic factors to MBC or articles with qualitative approach and in-depth interviews).
- Articles that affected other aspects of MBC disease including local epidemiological aspects and demographic patterns, studies of environmental risk factors or the effects of various drugs and medications or relationship between MBC and races, research into the mechanisms of MBC

tumors in cell level and in molecular subgroups or if a special or rare MBC tumor, etc.

– Articles that were studies of a certain group of people e.g. breast cancer in transsexual men or in HIV-infected men.
– Articles that were about MBC metastasis.
– Of the total of 812 articles, 187 were included in this review study that deals with genetic aspect, histopathology, and psychosocial aspects of MBC and also comparison between MBC and FBC.

III. Results and Discussion

a) Heritability and genetic aspects

The interaction between genetic and environmental factors generally, is probably of major importance for the occurrence of MBC (13). Most known risk factors related to genetic predisposition include positive family history, BRCA gene mutations and Klinefelter's syndrome (14).

Several studies indicate that a family history of breast cancer is associated with greater risk of MBC (15 -22). Approximately 15% to 20% of male patients with breast cancer have a positive family history (12-13). Quite a large percentage of MBC patients have a history of breast cancer in first-degree relatives (13, 19, 20, 23-27). A positive family history of either male or female breast cancer among first-degree relatives leads to 2-3 times higher risk of the emergence of MBC (9, 21, 23, 25, 28). This risk increases with increasing numbers of affected first-degree relatives and the early onset of breast cancer in the affected relatives (28). There is a strong correlation between heritable mutations in BRCA and the risk of MBC, but BRCA2 mutations are far more frequent than BRCA1 mutations in MBC cases (13, 27-32). BRCA2 mutations in MBC patients have been assessed in several studies and in various countries (13, 26-27, 33-47) and the results vary between 3% and 40% (Figure 1). These studies suggest that the frequency of BRCA2 mutations may reflect the possible genetic differences between different populations but caution should be exercised in interpreting these estimates, because of the small sample populations in the studies (9) or possible selection bias (18). The estimated lifetime risk of breast cancer among male BRCA2 mutation carriers is 5-10%, compared with a 0.1% risk of MBC in the general male population, i.e. 50-100 times higher (48). Moreover, the cumulative risk of MBC in BRCA2 mutation carriers is always higher than in non-carriers, and in all age-groups, but it is highest among those in their thirties (1,500 times higher) and in their forties (630 times higher) and lowest for those in their eighties (69 times higher) (28, 29). A recent multi-centric study from Italy by Ottini et al. (2012) (30) has shown that BRCA2 is correlated with aggressive tumour behaviour and with higher tumour grade.

Klinefelter's syndrome is also strongly associated with breast cancer in men (9, 33). The syndrome is characterized by a rare chromosomal abnormality, 47 XXY, with breast growth, small testes, infertility and increased excretion of follicle-stimulating hormone (FSH) (33), which occurs in less than one man per thousand (9) .The mean age of breast cancer patients with Klinefelter's syndrome is 58, which is slightly lower than the average age for other male breast cancer patients (9, 33, 50). Up to 7% of men with breast cancer may have Klinefelter's syndrome (33, 51-53). Compared with the frequency of the disease in the general population, breast cancer can be at least 20 times more common in these men (3, 9, 54). Other less known genetic mutations that have been reported in men with breast cancer include Reifenstein syndrome or androgen receptor (AR) mutations (55), CYP17 polymorphism (56), Li-Fraumeni syndrome or p53 or CHEK2 mutation (57 -59), Cowden syndrome or PTEN mutation (60) and Lynch syndrome or HNPCC (61), but the correlation between these mutations and increased risk of MBC has not yet been adequately researched (32, 62).

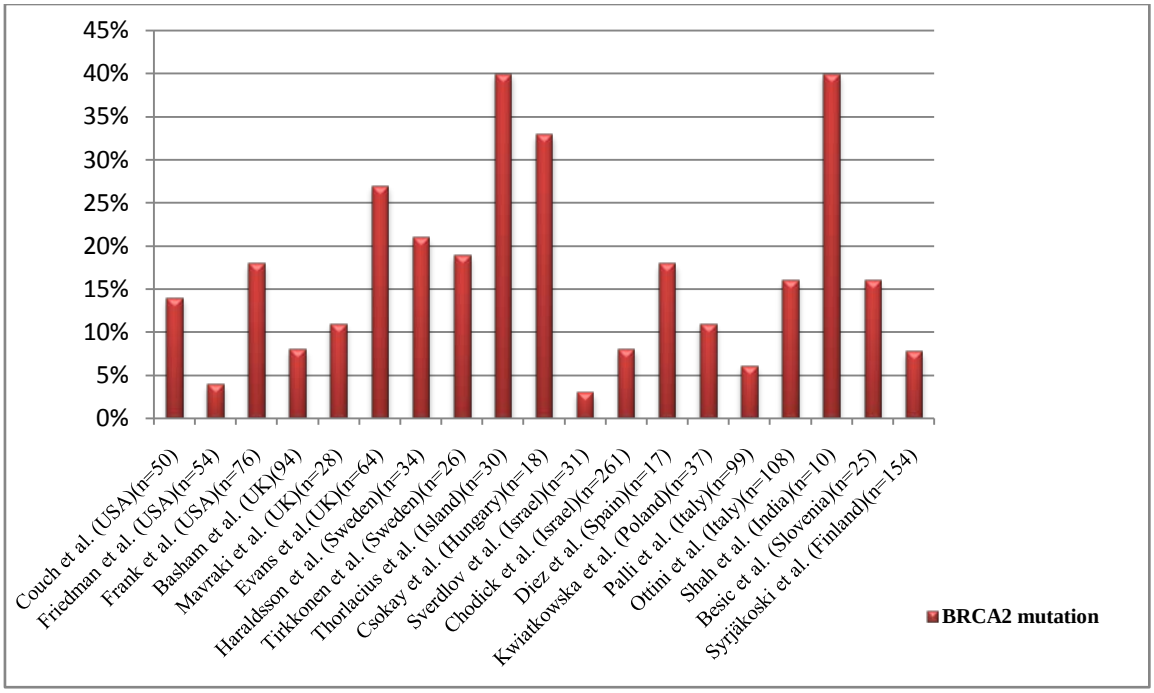

Figure 1 : BRCA2 mutations (%) in MBC patients in different studies and in different countries, with the number of participants in the studies

b) Histopathology

Almost all histopathological types of breast cancer have been identified in men (32, 63). The most common type is invasive ductal carcinoma, which is at least 80% in several studies (10, 14, 63-71) and ductal carcinoma in-situ (DCIS) is far less common, less than 10% (1, 63, 69, 72-74). A study by Lanitis et al. (2008) (75) showed that in-situ cancer in men is not as rare as reported in earlier studies, which indicates earlier detection of breast cancer in men (72). Rare tumour types include invasive papillary and medullary lesions (3) and Paget's disease (3, 62) and lobular breast tumours (3, 69, 76-78). Male breast tumours are usually sensitive to the hormones oestrogen and progesterone (10, 76, 79, 80, 81-87), which has been reported at between 55-92% for oestrogen and 39-89% for progestrogen for MBC cases in large, retrospective series (63, 69, 88-89) (Figure 2). Lymph node involvement in the armpit is very frequent, from 41% to 57% in large retrospective series (10, 90- 96) and 11-20% of male breast tumours grade I, 55-61% grade II and 22-33% grade III have been reported in large retrospective series (95-94, 81) Generally, 5-15% of MBC patients have metastases at diagnosis (6, 64, 76, 81, 97-98) but the numbers are higher in African and Asian series, i.e. up to 30% (71, 99-101). Details of the growth factor HER2 from various studies are highly variable and up to 56% of male breast tumours display an over-expression of HER2 (12, 43, , 57, 102-107).

c) Psycho-social aspects

The general perception of breast cancer as a female disease causes surprise in many men when they are diagnosed with breast cancer (77). France et al. (2000) (108) described in their study that men with breast cancer have been shocked to get a breast cancer diagnosis. These patients have not been aware that men can also be affected by such a disease, which is associated with femininity and they have found it difficult to understand that the disease can develop in a male body. Patients have also had difficulty revealing their breast cancer diagnosis to those around them. Iredale et al. (2005) (109) have described in their study that men with breast cancer are afraid of others' reactions, which reduce or question their masculinity. These patients were also uncertain about discussing this sensitive topic with those around them (109). However, when these patients try to talk about it with their friends and colleagues, the reaction becomes distrust and often a subject for fun in a lamentable way (77).

A sense of frustration also occurs due to a lack of relevant information about breast cancer in men (108-113). Men with breast cancer are more vulnerable in social contacts in comparison with female breast cancer patients (114), which leads to high levels of disease-specific stress (111). The cancer impact and cancer-related stress are worse in young MBC patients compared to those who are older (111, 115). Concerns about masculinity, fear of stigma and experience of isolation are associated with the general lack of knowledge and information about the disease (111). Different experiences of breast cancer care have also been reported by men and women in a study by Sime (2012) (116).

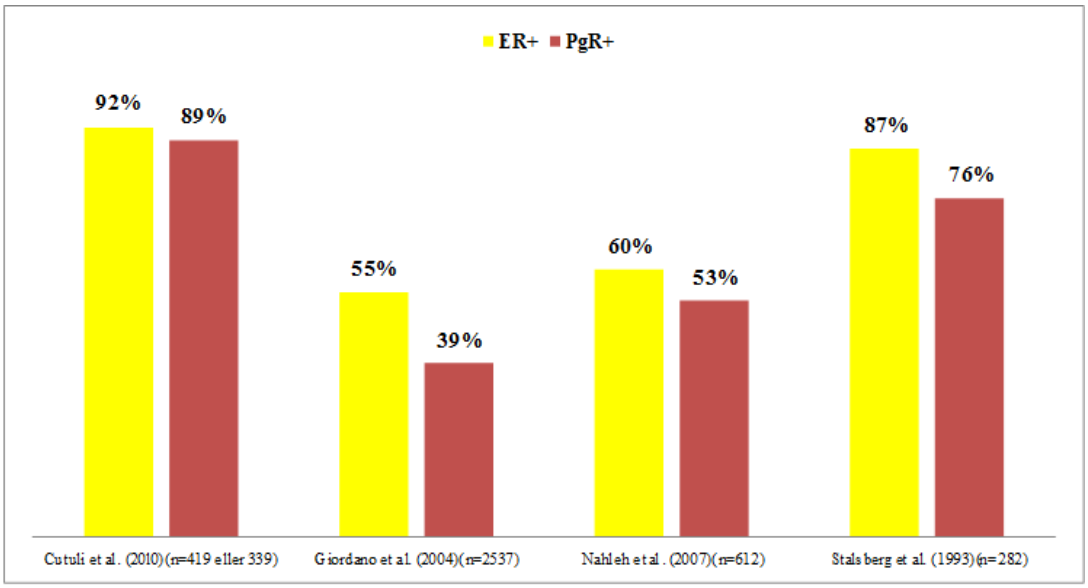

Figure 2 : Positive oestrogen/progesterone receptor (ER+ and PgR+) (%) in male breast tumours in some large retrospective series

d) Comparison between MBC and FBC

MBC and FBC differ mostly with regard to incidence figures, age at diagnosis, frequency of histological tumour types and frequency of expression of hormone receptors (5). The incidence of male breast cancer varies. Some studies report an increase in MBC in a few countries (4, 69, 77, 117-119). However, the incidence of female breast cancer (FBC) has been found to be increasing in most countries (50,102, 120) The incidence of breast cancer in men has been stable in Europe for several decades (121) and a new international population-based study by Miao et al. (2011) (120) also shows that male breast cancer incidence rates have remained at a stable low level during for the past four decades. Epidemiologically, MBC occurs continuously with a certain average frequency in the general population and is little affected by environmental factors, but conversely, FBC has a tendency to continuously increase, which may be due to the triggering effect of one or more environmental factors (122). Male breast cancer incidence is generally less than 1 per 100,000 population, in contrast to the much higher incidence of female breast cancer of 122 per 100,000 population (102), i.e. the incidence ratio between MBC and FBC is 0.008, but this ratio is higher among African Americans (123) and is fivefold in Africa, 0.042 (124). While the incidence of MBC generally exhibits a uni-modal distribution, with peak incidence at the age of 71 (50,125), the incidence of FBC tends to have a bimodal distribution (126, 80) with early-onset and late-onset incidence at 52 and 71 years of age (50). Age-specific incidence for men is steadily increasing either constantly (50) or exponentially (62), but increased age-specific incidence for women is rapid up to 50 years of age, but then at a slower pace after menopause (50). Differences in age-specific incidence between men and women reflect differences in underlying risk factors for the disease (102).

But on the other hand, the international correlation between male and female breast cancer incidence rates is quite strong (r = 0.69), meaning that both sexes have several common risk factors for breast cancer (102). Age-specific incidence patterns among men also display a biological similarity between male breast cancer and late-onset female breast cancer (127). This similarity shows that hormonal mechanisms are important (127) but the differences between them may reflect unique mechanisms that may be associated with androgens (18).

Several studies indicate that male breast cancer patients are, on average, 5 to 10 years older than female breast cancer patients at the time of diagnosis (69, 82, 89, 120, 122, 128 -132), but the age gap between men and women is likely to be less in the Middle East and South Asia (5, 133-136). The differences between men and women in the age presentation may also reflect gender differences in underlying risk factors, pathogens, and/or over-diagnosis (102).

In both sexes, a family history of breast cancer can increase the risk of developing this disease (15, 18-22). Genetically, MBC is distinct from FBC (43,137). BRCA1 and BRCA2 mutation genes give an increased risk of breast cancer in both sexes (14, 52, 138) but mutations in these genes do not increase the risk of developing male breast cancer at the same rate in women (139). While mutations in BRCA1 in women can give up to 80% lifetime risk of breast cancer, they do not cause as high a level of risk of breast cancer in men

(128). In women, between 30% and 86% of hereditary breast cancer has been estimated to be aetiologically linked to BRCA1/2 gene mutations, but estimates of these mutations in MBC are significantly smaller (9). Several studies on men with hereditary breast cancer have shown that BRCA1 mutations are significantly less common (26, 27, 37, 42, 140) but many studies show that BRCA2 mutations play a particularly prominent role in the development of breast cancer in men (13, 26, 27, 39, 40, 43, 46, 48, 139-146) BRCA2 mutation also seems to have a stronger role in MBC development than in FBC development in younger people (13, 36). It is also suggested that male breast cancer has a higher genetic than female breast cancer (147).

The relationship between MBC and CBC (contra-lateral breast cancer) is much stronger than the relationship between FBC and CBC i.e. 30 times increased risk of CBC in men, compared to 2-4 times increased risk of CBC in women (28).

Histologically, it is impossible to distinguish between MBC and FBC (14). Almost all the histological breast cancer types described in relation to FBC have also been reported in relation to MBC (12). In both sexes, invasive ductal carcinoma (IDC) is a very common form of breast cancer (8, 65 149-152). But IDC is more common in men than in women (5).

When we look at percentages, non-invasive, in-situ breast cancer in men is not higher than is seen in women before the introduction of mammography screening and it may depend on the size of the male breast, which simplifies the detection of small breast lumps in men using clinical breast examination (63). Papillary breast cancer is relatively more common in men(8,89) i.e. 2% to 4% in men compared with 1% in women (49), but lobular carcinoma is less common in men because of the absence of the mammary glands in the normal male breast (8, 69, 76,78, 81,89-90) Even rarer subtypes of breast cancer, such as medullary, tubular and mucinous types, have been reported in men, although the male equivalent may be somewhat more unusual than the female (6, 63, 64, 81). Inflammatory breast cancer and Paget's disease have been seen with similar levels of frequency in men and women (10, 63). Male breast tumours have a significantly higher frequency of hormone sensitivity, with regard to oestrogen and progesterone, than their female counterparts (85, 103, 107,127, 135, 153-161) which implies a different pathogenesis in the development in of this disease (87). Such differences may play key roles in the therapeutic treatment, which should be grounds for different treatment strategies in comparison with female breast cancer (87).

Older studies show that in contrast to women, the frequency of hormone sensitivity in men does not increase with age (63). But a new study by Giordano et al. (2004) (69) has shown that there is a strong link between this hormone sensitivity in male breast tumours and their age, in the same way that has been observed in women. Oestrogen receptor positivity in males may be a result of the low level of circulating oestrogen in the male body, which is similar to that observed in women after menopause (62). In contrast to this interpretation, several researchers suggest that sexually reducing endocrine condition and/or increased oestrogen production may be the underlying hormonal pattern in MBC cases (162). The amount of testosterone that is converted to oestrogen by aromatase is much greater in men than in women, regardless of a woman's menstrual status, which may explain the differences in approach and response with regard to hormonal treatment of MBC and FBC (163).

HER2-positive breast cancer in men is less common than in women (33, 164-165) which is more correlated with higher cancer stage and with higher histological grade (33). There are several similarities in clinical signs and symptoms of breast cancer in both sexes (73), such as a hard and fixed lump in the breast, with skin or nipple retraction, and nipple discharge and enlarged lymph nodes in the armpit (166). But in MBC, it is more common for the nipple to be affected (76, 131,167) because male breast tumours develop just below the nipple, where rudimentary milk ducts are located, and not in the upper lateral quadrant of the breast, which is characteristic in women (33). Self-detection is the primary form of detection among men, both with cancer in-situ and with invasive breast cancer. However, ductal carcinoma in situ (DCIS) in women is usually detected through screening (168).

Compared to FBC lesions, the edges on MBC lesions are often more defined and calcifications are less frequent and coarser (33, 169), Micro-calcifications occur mainly in ductal carcinoma in-situ (DCIS), which is rarer in men (33,73, 170) Cancer metastases in the lymphatic tissue of the skin are far more common in male breast cancer compared with female breast cancer (136).

Men undergo mastectomy more often than females (171, 172). Men who have undergone mastectomy are more likely than women to receive radiotherapy (95, 168, 173) because of more advanced disease stage and/or more nipple and skin involvement (62). Men are also less likely than women to receive chemotherapy after surgical treatment (173).

FBC prognosis is correlated with patients' age at diagnosis, but conversely, there is no association between age at diagnosis and MBC prognosis. Relative cancer survival in women increases from 35 years of age to age 45-49, and then decreases to the age of 50-59 and then increases again after the age of 65. This means that relative cancer survival in women is a function of age at diagnosis, but relative survival in men has no significant link with age at diagnosis (174).

Compared to women, cancer survival in men is lower, especially in regions where women are routinely

examined with mammography (49). This is because of a more advanced stage of disease at presentation, with higher incidence of lymph node involvement (7, 67, 131) and the low standard of loco-regional treatment for MBC has a significant role for the poorer results (120).

Several studies have shown that survival in MBC patients is almost equal to the survival of FBC patients if the age and stage of disease at diagnosis are matched (50, 69, 83, 161, 175-177), and after adjustment for age at diagnosis, the stage of the disease and the treatment methods, men have actually had significantly better survival from the disease than comparable women (120). A matched analysis of male and female breast cancer patients in a German study by Foerster et al. (2011) (178) has also shown that the 5-year disease-free survival rate was 53.4% (95% CI, range from 54.1 to 66.3%) in men and 62.6%. (95% CI, range from 63.5 to 75.3%) in women, which was not a significant difference ($p > 0.05$), and the 5-year overall survival rate was 71.4% (95% CI, range from 62.1 to 72.7%) in men and 70.3% (95% CI, range from 32.6 to 49.6%) in women, which was also not a significant difference ($p > 0.05$). Xia et al. (2010) (179) have shown in their study that the 5-year and 10-year overall survival rate between Chinese men and women in general are not equal, and that Chinese men have poorer survival rates compared to Chinese women, but when the male group was compared to post-menopausal women, the difference disappeared. In their population-based cohort study, Thalib & Hall (2009) (180) have shown that gender has no significant effect on the prognosis, which was confirmed in a large retrospective study by Hill et al (2005) (181) when 2,923 male breast cancer cases were compared with 442,500 female breast cancer cases. With respect to the variables tumour size, lymph node status, age at diagnosis, histological grading and receptor status, no significant difference has been demonstrated in survival rates for male breast cancer patients compared with female patients in a multivariate analysis in a study by Borgen et al. (1997) (156).

Nahleh et al. (2007) (89) showed in a multivariate analysis that not only tumour size and lymph node status are independent prognostic factors for survival in men, but that gender also serves as an independent prognostic factor. Median survival age between men and women had significant differences when patients have breast cancer at stages I and II, but this difference disappeared at stages III and IV. It was also shown that MBC patients with negative lymph node status had shorter median survival age than FBC patients with the same lymph node status, but this difference also disappeared when both genders had positive lymph node status.

A new study by Ioka et al. (2006) (136) also showed that the 5-year survival rate only decreases with increasing age in men, and that male breast cancer patients have significantly poorer 5-year survival rates compared with women at a corresponding stage of the disease, which is also confirmed in several recent studies (171,182-184) Deaths due to primary breast cancer in men is higher than in women, which is also reported in a study of Gnerlich et al. (2011) (185) and this mortality rate has not changed, unlike female breast cancer (117). It should be emphasised here, the importance of adjuvant systemic therapy, mammography screening, and reduced use of hormone replacement therapy for decreasing mortality among women with breast cancer (127).

The gender difference for prognosis may be a result of anatomical differences between the male and female breast, i.e. undeveloped breast tissue in men facilitates the spread of tumours to the lymphatic tissue in the skin and early regional and distant metastases, both on the overlying skin and on the underlying chest muscle (76) and possibly depends on the biological differences between male and female breast tumours (182, 184) or on a result of the lack of adjuvant systemic therapy (chemotherapy and/or hormonal therapy) (183) or on the effect of co-morbidity and other primary tumours that act as confounding factors (179). With overall survival as a benchmark for comparison, there is no difference between MBC and FBC prognosis in several studies. However, with disease-specific survival as the benchmark for comparison, the same study shows a significant difference between the two groups (176,179).

It is still unclear whether the MBC prognosis is worse than the FBC prognosis, so there is a need for multi-centric prospective studies in this area (177). One should focus on identifying prognostic factors and on defining optimal therapy for MBC patients (173). Psychological differences between male and female patients with breast cancer are also grounds to introduce a different treatment strategy, especially with regard to hormone replacement therapy (117). An early diagnosis with the absence of lymph node involvement has a significant role in improving the outcome of MBC treatment (188).

IV. Conclusion

A significant advance in understanding MBC can improve MBC diagnosis and prognosis. The treatment of MBC has been extrapolated from knowledge available about FBC, although there are many differences in pathogenesis, in biology and in genetics for these two diseases, especially with regard to differences in the role of hormone oestrogen in MBC compared to FBC.

An increased understanding of the potential differences between male and female breast cancer is important, because this can provide new opportunities for therapeutic intervention and probably improved outcomes for MBC treatment. Increased awareness about breast cancer in men will also increase the

chances of early detection and result in improved prognosis. Clearer treatment guidelines are also necessary in order to improve MBC prognosis. Increased input is needed for informative and psychological support for MBC patients and public education should be oriented toward men at higher risk to reduce symptom duration before diagnosis.

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The use of Reconstructed 3D Brain Surface Imaging Approachto Identify the Precentralgyrus and Its Detail Function Distribution

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Abstract- *Objective:* To study the use of reconstructed3D brain surface imageto identify the precentralgyrus and its detail functionaldistribution.

Method: There are a total of 12refractory epilepsy caseswhich need intracranial electrode implantation according to a preoperative assessment. In these patients, magnetic resonance imaging (MRI) and functional MRI (fMRI) were conducted pre-operation, and a cranial computed tomography (CT) scan was performed after electrode implantation. BrainVoyager software was used for 3D reconstruction of the brain surface by using MRI data, which was integrated with the subdural electrode CT. Based on the characteristics of the shape of the precentralgyrus, the precentralgyrus was marked in the reconstructed brain surface image, and the precentralgyrus and adjasentgyrus were found and identified in the surgical field by comparingthe typical shape of the exposed gyrus in the reconstructed3D brain surface image with that in theintraoperative photographs. The reliability of the precentralgyrus identified by the presentmethod was verified by electrical cortical stimulation (ECS) and fMRI.

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Results: All the 12 cases were performed 3D brain surface reconstruction and precentralgyruswas found and marked according to the characteristics of precentralgyrus. There were 101 electrodescovering the precentralgyrus and 73 (72%)of them had motor response to electrical stimulation. In the contrast team, (the area which is 1 cm ahead of the precentralgyrusidentied by the reconstructed3D brain surface), the motor response rate was 13% (17/130) ($p<0.05$). During fMRI, 100% of the precentralgyrus and 58% (7/12) of postcentralgyrus was activated during hand movement,with no activation of the areas ahead of precentralgyrus, so there was also significant difference between precentralgyrus and gyrus ahead. Therefore, the precentralgyrus identified by the presentmethod is accurate and reliable.

Conclusion: It is simple and feasible to identify the precentralgyrusby using the 3D reconstruction of brain surface image.

I. Introduction

During surgical procedures, identifing the precentralgyrus and then protecting the motor function are crucial for neurosurgeons. However, it is very difficult to accurately find and confirm the precentralgyr-usbyanatomic landmark without the aid of navigation or electricalcortialstimulation. The precentr-algyrus is challenging to be identified mainly due to limited exposure, which leads to a lack of an overall impression regarding the shape of the gyrus. Intraoperative blood vessels and gyrus variation also make it difficult to precisely identifythe gyrus.

Reconstruction and representation of the cerebralcortex from magnetic resonance imaging (MRI) plays an important role in the study ofthe structure and function of the brain [1—6]. In recent years, there has been a significanteffort towards the development of methods for the cortical surfacereconstruction.

Althoughthe 3D reconstruction of the brain surface has been applied to numerous types of research, to date it has not been used to locate the precentralgyrus, or to locate and protect the motor function area. Electrical cortical stimulation is a standard method to identify theimportant functional areas of the brainfor patients who need to be awakeduring surgery or patients with subdural electrodes[7,8,9,10]. However, it requires multi-point and multi-parameter stimulation (i.e. intensity, frequency and wave width of electric currents), and consequently it is laborious, time consuming and requires patients'cooperation with various tasks. According to previous reports[11,12,13], 71% of patients experienced after-discharge and other side effects by electrical stimulation, which affected the accuracy of positioning[14]. And a false positiveres-ponseby electrical stimulation will lead to incomplete resection of epilepsy foci, while a false negative responsewill lead to an unexpected loss of function. A hematomaunder the subdural electrodes or brain edema post intracranial electrode implantation-ncausing inhibition or loss of function of local cortex, will result in a false negativeresults by ECS. And false positive results by ECS occur in cases with larger electric current or increased excitability of focal cerebral cortex causing the distant spread effect.

fMRI is another common noninvasive method for preoperative functional positioning[15,16,17,18,19]. fMRI provides useful detailed assessment of anatomic features, including deep brain structures. However, the repeatability of functional positioning remains a challenge [20], and the results are not always consistent with invasive examination. At the same time, it also

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requires patient's good cooperation to complete relevant tasks.

Without the results of fMRI or electrical stimulation for functional positioning, it is difficult to identify and protect the patient's precentralgyrusin the condition of limited exposure, if the epileptic foci is close to the precentralgyrus. It is also a challenge to quickly and accurately locate the patient's precentralgyru-sintraoperation. Therefore, there is an urgent clinical need for an ideal and simple positioning technique to identify the precentralgyrus. With the development of the 3D brain surface imaging technology, positioning and identification of the precentralgyrus can be applied in clinical practice. The present study aimed to identify the precentralgyrus according to the characteristics of the precentralgyrusby using the technique of the 3D brain surface reconstruction.

II. Methods

Twelve patients (8 female, 4male,mean age 21.4 years), with refractory epilepsy, who required implantation of intracranial electrodes (subdural and deep electrodes) in the frontotemporaland central region according to preoperative assessment, were enrolled. Functional positioning was conducted during the inter-ictal when the patient was in a good condition without seizureat least one hour before and after the test. Patient characteristics including seizure frequency and electrode coverage are shown in Table 1.

Table 1 : Clinical data

patient	Sex	Age	Onset	MRI	Seizure types	Seizure fre.	EEG	Grid	Resection area	Englegrade	No. subdural Electrodes	hemiplegia
1	F	25	8	N	CPS,GTCS	2-3/w	F4F8T4	RF,RT	R-FP,RT	II	64	no
2	F	21	4	N	PS,GTCS	1-3/w	FP2F4F8	RF,RT	R-IFG,SH	I	64	no
3	F	22	1	N	PS,GTCS	2-3/m	FZ,F4	RF,RC	R-C,R-SFG	I	64	yes
4	F	23	14	N	PS,GTCS	4-6/m	C3T3	LF,LC	LC	I	64	yes
5	F	28	9	N	CPS,GTCS	1-3/w	F4F8FP2	RF,RC	R-MFG	I	64	no
6	M	23	6	N	CPS,GTCS	3-5/m	F3,F7,SP1	LF,LT	L-IFG	I	64	no
7	M	10	7	N	CPS,GTCS	1-3/m	F8,F4,T4,FP2	RF,RT	R-MFG	I	64	no
8	F	19	6	N	PS,GTCS	1-3/m	F3,C3	LF,LC	LC	I	80	yes
9	F	21	7	N	PS,GTCS	4-7/m	F4,T4,P4	RF,RC	RF	I	80	no
10	M	27	5	N	CPS,GTCS	2-6/m	F3,F7,SP1	LF,LC,LT	LF	II	96	no
11	F	16	8	N	PS,GTCS	4-6/w	C3T3	LC,LT	LC	II	64	yes
12	M	22	12	N	CPS,GTCS	1-2/m	F3,F7,	LF,LC	LC	I	80	yes

a) Electrical stimulation

Long term electroencephalography (EEG) was used to record intracranial EEG (Bio-Logic, San Carlos, USA;1024 h/channel, 0.1-134Hz smoothing). A strip with 4 electrodes were placed under the skin for reference. When enough seizures had captured and patient in a good condition, function mapping were done usingECS. 60Hz biphasic pulses lasting for2-5s were delivered by an Ojemann Cortical Stimulator onto the selected pairs of electrodes. Thecurrent intensity of the stimulation started from 2mA and was gradually increased until patientsshowed or reported symptoms related to sensory motor cortex or the stimulus strength reached15mA [21].

b) Integration of 3D brain cortex reconstruction and intracranial electrode CT scan

Intracranial electrodes were integrated into the structure of the individual brain via the following steps: 1). Reconstruction: brain surfaces were reconstructed based on the T1-weighted images using theBrainVoyager software; 2). Register:post-implantation CT images were registered to the reconstructed

brainsurface. We employed a mutual-information-based linear transform to align the MRI and CT in3DSlicer software [22].3) The 3-D brain surface was overlaid with semitransparent CT images using our in-house registration toolbox.The course can be completed in 30 minutes. The electrode position was compared to intraoperative photographs, and the registration error was less than 3 mm according to some anatomical marks. Figure 1C

c) Identification and marking of the precentralgyrus

According to the anatomical features of the brain gyri, the central sulcus and the precentral sulcus were set as front and back borders, and the shape was parallel to the coronary position. From the lateral fissure extending upward to the longitudinal fissure, it continued backward to the postcentralgyrus.The superior frontal gyrus, middle frontal gyrus, inferior frontal gyrusends at the precentralgyrus and is vertical to it. The inferior frontal gyrus ends and integrates into the bottom of precentralgyrus, middle frontal gyrus ends and integrates into the middle of precentralgyrus and the superior frontal gyrus ends and integrates into the top of precentralgyrus which is near the longitudinal fissure. Figure 1A

After the reconstructed 3D brain surface image was integrated with subdural electrodes, we drew the range of the precentralgyrus using a black line in FOTOSHOP through direct visual comparison. (Figure 1BC)We then marked on the numbers and points of electrodes that covered the precentralgyrus, and identified the neighboring gyri, which mainly included: postcentralgyrus, superior frontal gyrus, middle frontal gyrus, and the inferior frontal gyrus.

d) Comparison of brain surface imageand surgical photos, tags for gyri confirmation

During surgery, precentralgyrus and other gyri were identified in the photos based on typical characteristics of gyri's shape (usually use precentralgyri) by comparing the 3D brain image with the surgical photos.Furthermore, we can take the subdural electrodes as reference to identify gyrus.So the 3D brain surface image led to clear exposure of anatomy and function of gyri one after another in the operating field.(Figure 1D)

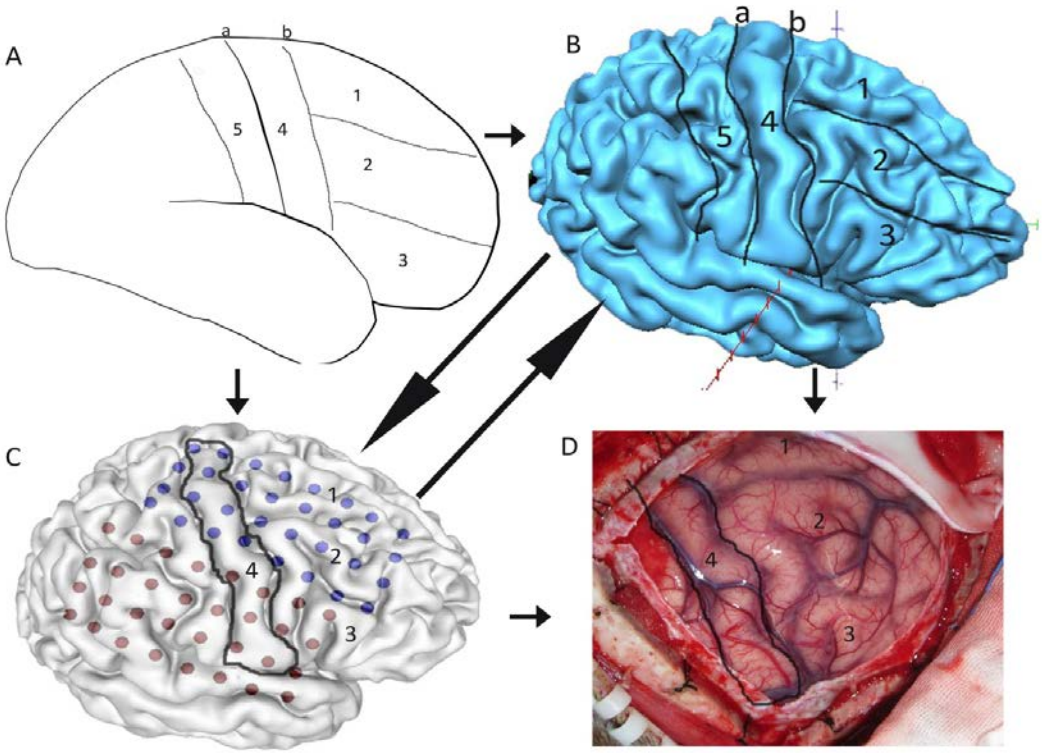

Figure 1

e) Verification for electrical stimulation

Electrical stimulation locates the precentralgyrus and verifies the identification of precentralgyrus by brainsurface image. When electrical stimulation is conducted, the precentralgyrus demonstrates the most obvious motor response from the frontal pole backward. The electrodes which produced a motor response to the electrical stimulation were marked on the brain surface; it can be helpful to see whether the points appearing as a motor response were located on the precentralgyrus.

These points appearing as a motor response can be classified as either within the precentralgyrus or outside the range of the precentralgyrus.

The proportion of motor response points in all electrode points on the precentralgyrus was calculated (between 0 and 1). A percentage closer to 1 indicates that the positioning of the precentralgyrus is more reliable. In the contrast team, precentralgyrus move forward 1 cm(i.e.2electrodes aheandprecentral sulcus), the percentage of motor response points was also calculated.(Figure 2,Table. 2) The reliability of our method for locating the front border of the precentralgyrus can be verified statistically by comparing the motor response in the two areas. The posterior border extending backward 2 cm should be in the position of the postcentralgyrus, which is also an important functional brain region. This study did not focus on the position of the posterior border but identified the frontier border of the precentralgyrus, to ensure safety during surgery on epileptogenic foci at the back of the frontal lobe. There are three explanations for motor response points outside the precentralgyrus: 1.) caused by the spread of electric current; 2.) the abnormal or potential motor area or part of the sports network, and 3.) a false positive reaction due to movement by the patient at the time of stimulation.

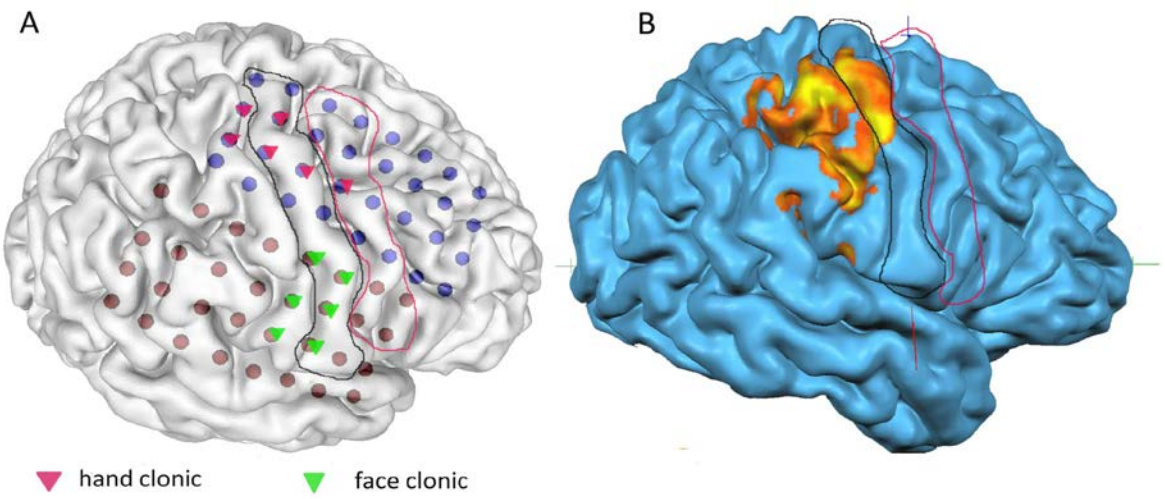

Figure 2

f) Process and positioning of fMRI

Patients performed three differentmotor tasks (i.e., left hand, right hand, tongue) in 12 second task blocks interspersed with12 second resting blocks. Each task blockcontained only one type of movement and therewere 6 blocks for each type of movement in the entire session.MRI was acquired using Philips Achieva 3.0, with the 8-channel SENSE head coils. Visual cues were presented during each task block using the Psychophysics Toolbox4.31. Structural images were acquired using a sagittal magnetization prepared rapid gradient echoT1-weighted sequence (TR 2s, TE 2.37 ms, flip angle 90°, slice number 180, 1-mm isotropicvoxels). fMRI were acquired using echo planar imaging sequences (TR 3s, TE30ms, slice number 47, 3-mm isotropic voxels). fMRI data were processed using SPM8(Wellcome Department, UCL). The pre-processing included slice timing correction, rigid bodycorrection for head motor, and normalization for global mean signal intensity across tasks.fMRI results were integrated with 3D brain surface image through BrainVoyage software to determine whether the brain region representing motor response was in the precentralgyrusas located by our method. (Figure.2, Table.3)

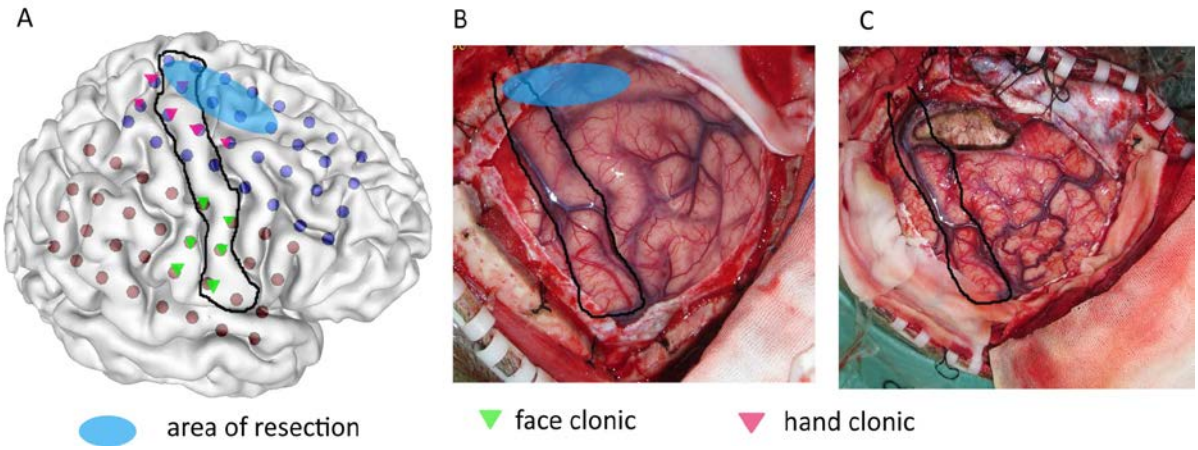

Figure 3

Table 2 : precentralgyrusverified by ECS

Group 1				Group 2		
patient	No.of electrodes in precentralgyrus(a)	No.ofpositive Electrodesby ECS(b)	Rate(%) b/a	No.of2electrodes ahead precentral sulcus(c)	No.ofpositvie electrodes by ECS(d)	Rate(%) d/c
1	4	2	50	10	0	0
2	5	3	60	10	0	0
3	12	7	58	12	1	8
4	13	10	77	12	2	17
5	5	4	80	12	1	8
6	7	5	71	12	1	8
7	11	8	72	12	0	0
8	8	6	75	10	2	20
9	10	8	80	12	4	33
10	8	6	75	8	2	25
11	12	8	67	12	2	17
12	6	6	100	8	2	25
Sum	101	73	72%	130	17	13%
t-test			P<0.01			

g) Functional mappingand epilepsy foci resection

All the 12 patients received epileptogenic zone resection.Acording toictal and inter ictal discharge byECoGmonitoring,the epileptogenic zone was found.The surgical plan was made.The resection area and function area was draw in the 3D brain surface and surgical photograph.We can predictwhether functional defectsoccurred post operation.(Figure 3)

III. Results

The precentralgyruswas marked in all 12 cases on the 3D brain surface image and theprecentralgyrus was identified in intraoperative photographs base onthe characteristics of gyrus in 3D image. The anatomy and function of brain gyri below theelectrodes which coveredboth exposed area and non exposed area was identified.

The precentralgyrus was found and marked in the 3D brain surface image according to its anatomical characteristics. There were 101 electrode sites on the precentralgyrus and 73 (72%) of these had a motor response to electrical stimulation. In the contrast team, in the area which is 1cm ahead of precentralgyrus, there were only 17 of 130 (13%) electrodes that had a motor response ($p<0.05$)(Table 2),demonstrating that there is a significant difference between the motor response to electrical stimulation in the area ahead of the frontier border of precentralgyrus (i.e., precentral sulcus) and the area behind it.

5 cases,in whichthe resection scope extended into precentralgyrusidentified by this method,developed hemiplegia of the hands and paralysis,but they recovered well half year later. (Figure.3) The other 7 cases, in which the resection scope was in front of the precentralgyrus, did not develop postoperative hemiplegia,although3of them had a motor response to ECS in the resection scope.

a) fMRI results

fMRI was performed in 12 patients, including finger movement of hands, the flexion and extension of toes and tongue movement, and 100% of the precentralgyrus was activated. All the activated

positions were located inthe precentralgyrus nearestto the central sulcus. 7/12 of the activated areas reached the postcentralgyrus, and no activation was foundin front of the precentralgyrus. Soprecentralgyrus was 100% activated, but the brain area ahead precentral sulcus was 0% activated.There was significant difference between precentralgyrus and the area ahead it. Therefore, the reliability of this method for locating the precentralgyrus was verified by fMRI.(Figure.2,table.3)

In addition, the precentralgyrus identified by the 3D brain surface reconstructionimage was consistent with electrical stimulation and fMRI positioning.

Table 3 : The reliability of the of precentralgyrusverified byfMRI

	Group1		Group2
patient	precentralgyrus actived by hand	Postcentral gyrus	Area of 2electrodes ahead precentral sulcus
1	+	-	-
2	+	-	-
3	+	+	-
4	+	-	-
5	+	+	-
6	+	+	-
7	+	+	-
8	+	+	-
9	+	-	-
10	+	+	-
11	+	-	-
12	+	+	-
rate	100%	58%	0%
$\chi 2$	P<0.01		

IV. Discussion

The positioning of precentralgyrus in brain surface image is very safety and reliable, and can locate the motor area both easily and simply. Also, it could give the whole scopy of motor area for protecting it. Therefore, it will avoid false negative results from positioning by ECS on the motor area. In addition, it is also the most reliable and safe method for protection of brainmotor function. And we were not worry about the resection of the area in front of precentral, because it generally will not lead to a lack of primarymovement. Although some patients with this area resectionmay lead to temporary lack of function of supplementary motor,they will recover very well later.In addition, our study do not focus on pathological shift patients, therefore in the absence of the anatomical shift, almost no primary motor area appears in front of the precentralgyrus, and few case reports show the existence of a variable motor area in front of the precentralgyrus, primarily due to the pathological shift[23,24].

Without pathological shift, the so-called variable motor activation area in front of the precentralgyrus (located by fMRI or electrical stimulation) is often a supplementary motor role, and it cannot cause irreversible loss and can quickly restore motorfunction. Characteristics of motor distribution in the precentralgyrus are clear, and motor function is distributed in various areas of the precentralgyrus. Until recently, only a few motor functions could be stimulated by ECS or tested by fMRI, such as limb and tongue movement, which are the most common functions. Thus, 3D brain surface positioning by precentralgyrus is both a safe and effective way to protect motor function, and the process is simpleand does not require the cooperation of patients. This method has clear advantages, particularly for patients who are unable to cooperate to perform the task of fMRI or ECS. It has been validated that this method is highly consistent with fMRI and ECS in positioning the precentralgyrus. ECS is used to verify the positioning of precentralgyrus in brain surface image, and the positive rate of ECS is high. In the contrast team, the positive rate with ECS was only 17% in the area two electrodes in front of the precentralgyrus, confirming the reliability of thismethod. Movement 3D-fMRI also demonstrated reliable positioning the precentralgryrus by our method. The activated movement area in fMRI is usually located to the side of the precentralgyrus near the central sulcus. The postcentralgyrus can also be activated. The motor area stimulated by ECS is mostly within the precentralgyrus, anda few extended to thepostcentralgyrus, but few located in front of the precentralgyrus, which may be related to current transmission. The slightdifference between the activation may be associated with the two motor reaction mechanisms. Subjects, who had spontaneous movementdruingmovement-fMRIscan, can have activation of proprioception, primary motor regions and associated motor regions of the brain. In contrast, movement stimulated by ECS is a stimulating movement, and such movement was the primary movement or supplementary movement. We need differentiate these two movement stimulated by ECS, because brain area of primary movement located

in precentralgyri,whereas supplementary movement located in supplementary motor area(SMA).

Based on the MRI scan, CT scan and intraoperative photographs, the whole process of reconstruction, integration and identification requires approximately 1 hour. This is less than the complex electrical stimulation operation, and unlike other methodologies there is no need for patient cooperation. The method used in this study to locate the precentralgyrus by 3D brain surface image, may be complementary and verification for electric stimulation and evoked potential, and also for high frequency ECoG motor function positioning (in the cases with subdural electrodes implanted).It can also be independently used to locate the precentralgyrus and to protect motor function during surgery in the situation when patients cannot complete electric stimulation or when subdural electrodes cannot be implanted.

There are several advantages associated with 3D brain surface imaging. It provided an easy method to confirm the sensorimotor area, and also provided a method to verify each other with ECS or fMRIin positioning sensorimotor area. In addition to the location of the functional brain areas, the corresponding anatomical gyrus can be easily located during surgery by comparing it with the shape of the gyrus, making location of the brain function more complete and comprehensive. For those cases that cannot complete electrical stimulation because of brain edema or bleeding in the brain after subdural electrode implantation, this positioning method is a viable alternative. It is also helpful in terms of epileptic foci localization. It can clearly and dynamically display EEG origin and spread, and evolution of symptoms of epilepsy coincides with anatomical function of the involved brain areas, which clarifies the mechanism of epileptic seizures and improves the accuracy of epileptic foci localization. Through visualization of electrode and brain surface, the surgeon's vision will be expanded and also recognition of anatomical features and functions of operated gyri will be improved. In addition, it also can found the false negative or false positive electrode identified by ECS or fMRI in movement function mapping. Therefore, it is a reliable guarantee for movement function because it gave the scopy of precentralgyrimore completelythan the methods of ECS or fMRI.

Rapid positioning will benefit the surgical plan. The main disadvantage of electrical stimulation is that it is tedious and lengthy. Electrical stimulation needs at least 10 to 20 pairs of electrodes to locate, and the electric current needs to slowly increase (1-10 mA). Therefore, just a simple test requires 1 to 2 hours. Not only ECS makes patients tired, but also there is risk that after discharge potentially inducing seizure, thereby preventing it from further positioning in danger point electrode testing [25, 26]. Therefore, this testing method is a challenge both for patients and doctors. In this study, we found that the function location can be completed in approximately 1 hour, with high safety and reliability. Electrical stimulation positioning can only test a pair of electrodes once, and the 3D brain surface image positioning can locate the whole precentralgyrus immediately,and also the testing time is significantly reduced, which is applicable to all patientsprovided they have had an MRI scan.

Brain surface imaging approach of positioning the precentralgyrus is very practical. Since the function distribution and arrangement of the precentralgyrus is becoming clearer, as long as the precentralgyrus is identified during surgery, then it is possible to gather detailed information of motor functiondistribution. (Figure.4). And the table.4 show the distance betweentdiffenent motor area in another 3 patents in our centre who receiced intraoperative electrical coticalstimulation. So we can get the detail distribution of motor function in the precental gyri. At the same time, if the precentralgyrus is set as a reference, partition and specific function of frontal lobe can be clearly marked, which can provide important guidance during epilepsy surgery. Thus the symptoms of epilepsy and the gyri involved can be connected and located, and surgeons have greater assurance for resection of the epilepsy foci. On the contrary, electrical stimulation positioning by subdural electrodes can only locate brain areas which arecovered by electrodes, and the function of the areas without electrode coverage cannot be evaluated. Becauseepilepsy foci often sets gyrus as a boundary, and the range of the resection may be extended to areas without electrode coverage, or extended to the unexposed areas. Therefore, there is no doubt that the 3D imaging approachhas greater advantages for identifying the gyrus as well as assessing the associated function. In some cases, there may be difficulties or uncertainties to identifythe precentralgyrusby 3D brain surface image. Then, we need overlap themotor activated fMRI results on the 3D reconstructed brain surface image, which can also help to find the precentralgyrus on the 3D constructed brain surface quickly and precisely.

In conclusion, it is both feasible and reliable to identify the precentralgyrusby using 3D brain surface imaging technique. Also, it can confirm and protect precentralgyrus in epilepsy surgery without needing intracranial electrodes implantation. In cases with subdural electrodes implantation, it can also help to overcome the limitation of exposed surgical field and the subdural electrodes, and ease the difficulty of gyrus identification, which is important to protect functional areas and to resect epilepsy foci.

Table 4 : The distance between different motor area

Patient	Tongue-mandibular mm	mandibular-mouth mm	mouth-eyelid mm	eyelid-neck mm	thumb-fore-middle finger mm	fore-middle finger-ring mm	Pinky-wrist mm	Wrist-shoulder mm
1	6	5	8	6	6	6	7	5
2	5	5	7	7	5	6	7	6
3	6	7	7	6	7	7	6	6
average	5.7	5.7	7.3	6.3	6	6.3	6.7	5.7

There were 3 patients results of intraoperative direct corticalstimulation.The above table show the distance between different motor area on the precentralgyri.Acording these data ,we can get the detail information of motor functiondistribution like figure.4.

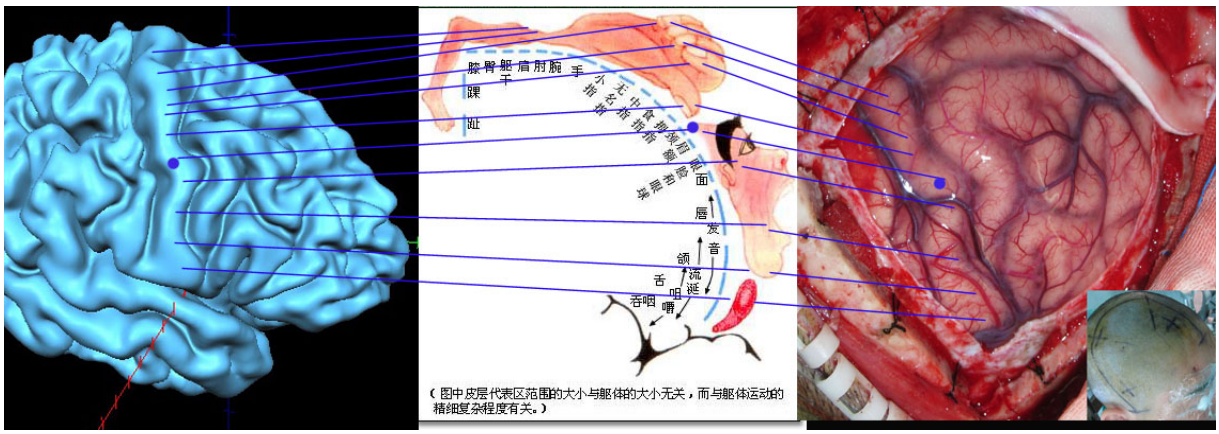

Figure 4 : detailed information of motor functiondistribution

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Diagnostic Value of Histopathology, Radiography and Computed Tomography for Diagnoses of Canine Osteo-Arthritis

By Ikhlas Abdelaziz Hassan, Mohamed Elfadil Mohamed, Osman Saad Ali, Caroline Edward Ayad, Hessain Ahamed Hassan, & Ahamed MustafaAbu Kona
Sudan University of Science and Technolopgy, Sudan

Abstract- Osteoarthritis is a common orthopedic problem in the small animals patients. In most cases, the degenerative changes in the joint are secondary to some predisposing cause. The objective of this case study was to assess Diagnostic Value of Histopathology Radiography and Computed Tomography for Diagnosis of Canine Osteo-arthritis The study was conducted in Police Dogs Administration (Ministry of Interior, X-ray Department), included Female German Shepherd dog which diagnosed radiographically for hip dysplasia and osteoarthritis. Using conventional radiography and CT images It concluded that conventional radiography is the most common method used to evaluate osteoarthritis, there has been an increase in the application of other imaging technologies (CT) during the past several years. These modalities and thehistopathology can provide the clinician with additional information that can improve case management.

Keywords: radiography, computed tomography, diagnoses, canine osteo-arthritis.

GJMR-D Classification : NLMC Code: WN 180, WN 206

Strictly as per the compliance and regulations of:

Diagnostic Value of Histopathology, Radiography and Computed Tomography for Diagnoses of Canine Osteo-Arthritis

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Keywords: radiography, computed tomography, diagnoses, canine osteo-arthritis.

I. Introduction

Osteoarthritis is the most common rheumatic disease encountered in small animal practice. No longer is osteoarthritis regarded as a simple consequence of aging and cartilage degeneration, but rather, the pathologic changes of osteoarthritis may result from active biochemical and biomechanical processes partly due to disturbances of the homeostatic mechanisms of anabolic and catabolic pathways. As to the cause of osteoarthritis, there is no etiology and its cause may be multifactorial. While there are many initiating causes, osteoarthritis is an irreversible process that often results in an end-stage clinical syndrome of the joint. Osteoarthritis exhibits varying degrees of severity, ranging from a mild, intermittent condition that causes mild discomfort and minimal disability, to a clinical state characterized by constant pain and severe disability. Clinically, osteoarthritis can be a challenging diagnosis to make. The disease is typically a slowly progressive problem. Consequently of the wide range of presenting signs, osteoarthritis is likely one of the most underdiagnosed syndromes in dogs and, especially, in cats.(1,2) It afflicts at least 20% of the canine population at any time.(1,3) This translates to roughly 10 to 12 million dogs in the United States.

There are no accurate estimates of the number of cats with osteoarthritis. A single definition of osteoarthritis remains elusive.

At a 1995 workshop, the American Academy of Orthopaedic Surgeons proposed the following consensus definition: Osteoarthritic diseases are a result of both mechanical and biologic events that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes, extracellular matrix, and subchondral bone.Although they may be initiated by multiple factors, including genetic, developmental, metabolic, and traumatic factors, osteoarthritic diseases involve all of the tissues of the diarthrodial joints.

Ultimately, osteoarthritic diseases are manifested through morphologic, biochemical, molecular, and biomechanical changes in both cells and matrix that lead to softening, fibrillation, ulceration, articular cartilage loss, sclerosis and subchondral bone eburnation, and osteophyte production.When clinically evident, osteoarthritic diseases are characterized by joint pain, tenderness, movement limitation, crepitus, occasional effusion, and variable degrees of inflammation without systemic effects.(4) For simplicity, think of osteoarthritis progression in three broad stages.(5) Research also has shown some continuity between bone and cartilage changes in osteoarthritis, suggesting an interaction between these tissues.(6)

II. Case Presentation

The study was conducted in Police Dogs Administration (Ministry of Interior, X-ray Department). included Female German Shepherd dog which diagnosed radiographically for hip dysplasia and osteoarthritis. Using A Poly mobile Siemens X-ray Machine was used. It has 2.5 KW output, with a KV range 40 – 100 in 21 Steps, and mA range 100 – 200. The exposure time mm–8 max. 5s. The X-ray tube has fixed anode tube 100/ 20 and focal spot 1.4 IEC – 336/ 1982. The anode angle is 14° and the inherent filtration is 3.2 mm aluminum equivalent value and weight153 Kg (Siemens, 2003), with Exposure factors(kV: 66,mAs:

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12.5,Film: 12x12 inches,Green Kodak X ray film,FFD: 100 cm)

The Kodak green X-ray film of size 12 × 15 inches was placed on Kodak medical X-ray cassette 12 × 15 inches with Kodak green 400 screen. A grid was used with a grid ratio 10/ 1 to improve the image quality. Focal distance 100 cm and grid lines 34 lines/ cm. Right and Left metal marker was used as an identification device. A three lead aprons were used for radiation protection. Digital camera model (E 4600, Size: 340 Kb and type: JPEG), was used for photographic purposes.The film was processed using automatic processor (Kodak x Omat 2000).

Histophology was done and shows that there is no change at the level of bone cells. However there are poly morph cells ,andmost of themarelymphocytewhich indicate chronic inflammation.

pelvic radiography including Ventro-dorsal extended view external rotation(VD2)projection,Dorso-Ventral flexed hips and knees(DV) projectionand CT Studies were done

III. Results

Conventional radiography is an excellent imaging technique for imaging bony structures but is a limited method for imaging soft tissue structures. It displays a greater spatial resolution than either MRI or CT. The disadvantage is that, the two dimensional displays of three-dimensional structures, results in superimposition that can obscure important findings. Details that can be derived from plain radiographs include information on the size, contour, density, and location of changes that are present in or around the joint. The areas that can be evaluated include the subchondral bone plate, trabecular subchondral bone, articular margins, and areas where ligaments, tendons, and the joint capsule is attach. Figures (1,2)

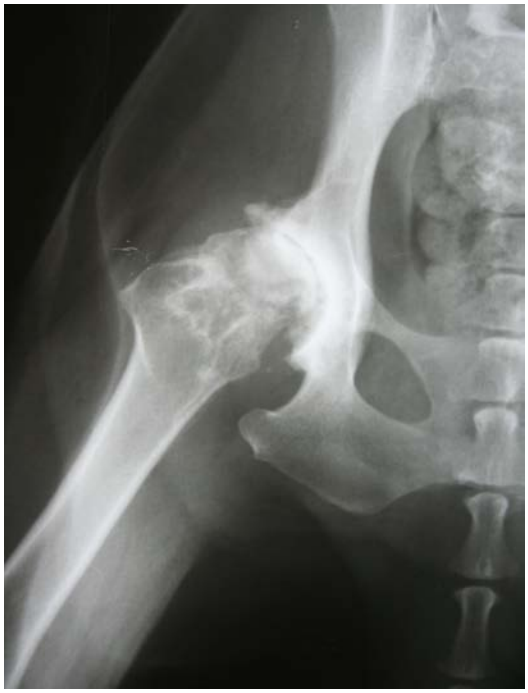


Figure 1 : Radiograph of Ventro-dorsal extended view external rotation shows shallow acetabulum, degenerative changes of the acetabulum , head of femur , greater and lesser trochanter marked in the Right and mild in the Left, absence of the right joint space, tight joint, no laxity, and marked osteoarthritis

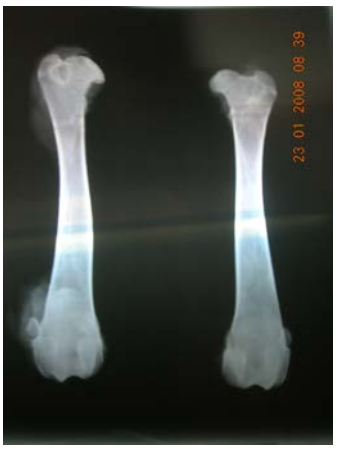
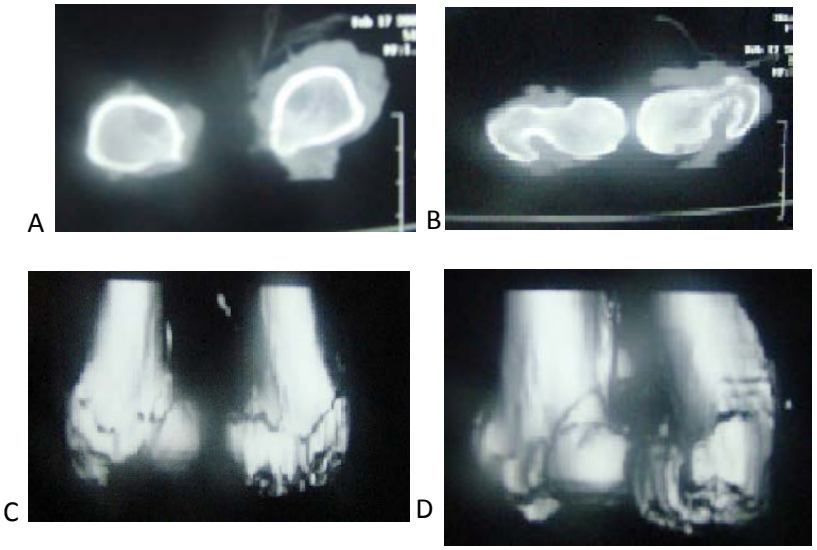


Figure 2 : Shows X-ray radiograph for both femurs (post mortum)

Computerized tomography (CT) has been introduced in the seventies in human medicine and has been more readily available to veterinarians over the last decade. It is a cross-sectional imaging technique using x-rays and computers. Better soft-tissue differentiation and absence of superimposition are the major advantages of CT over conventional x-ray techniques. Although the spatial resolution of CT images is poorer when compared with classical film-screen radiography. The cross-sectional image displays a superior discrimination of tissue attenuation enables differen-tiation of soft tissues structures that can not be perceived on

conventional radiographs. Subtle new bone formation and bone lysis are better identified on CT images when compared with conventional radiography because of their greater physical density discrimination,and the ability to manipulate the grey scale of the digital image, along with the elimination of overlying structures. Whilea loss of 30% of bone density is often required for a lesion to be visible on conventional radiographs. CT is able to detect density changes of only 0.5–2%. Another advantage is that the transverse CT images can be reformatted in multiple anatomic planes. In the stifle, compared to radiographic examination, Figures (3) (A, B, C&D), figure4.



Figures 3 : (A.B.C,D) CT images(A,B) shows CT scan Axial cuts of proximal ends of both femurs of 8 years German Shepherd canine, the left femur is normal but the right is affected. (C, D) shows: (3D) three Dimensional CT image of proximal ends of both femurs

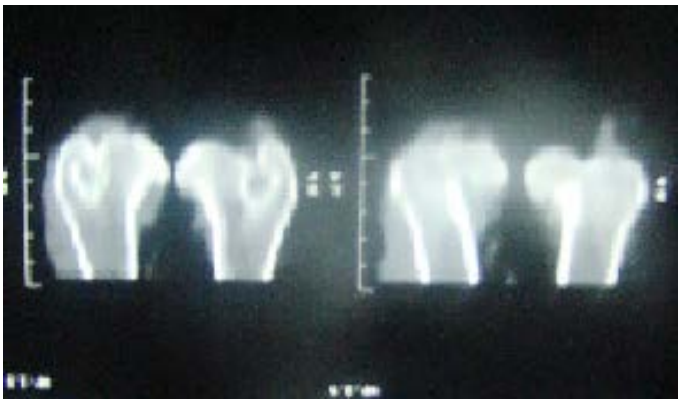


Figure 4 : Shows reformatted coronal view of proximal ends of both femurs

IV. Discussion

Generally, plain radiography has been in many cases the only imaging modality for the diagnosis and follow-up of stifle abnormalities. Over the years, however, radiologists and orthopaedic surgeons became aware of the importance of the diagnosis of not only bony conditions, but also of a diverse variety of soft-tissue conditions. Besides plain radiography, the veterinary profession nowadays gets access to the following imaging modalities: scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). Also arthroscopy has moved into the interest of veterinary orthopaedic surgeons for diagnosis and treatment of several stifle diseases and has become a routine procedure in several orthopaedic clinics.

In this case, conventional techniques like radiography are excellent methods to investigate morphologic changes in bones (figure(1). In people and horses joint space narrowing has been a well-accepted indicator of articular cartilage degeneration and is considered as a cardinal radiographic feature of disease. In small animals the loss of joint space is not a reliable sign as the radiographs are taken non-weight-bearing. Individual soft tissue structures are not visualised as easily as the bony structures unless they are bordered by fat . Indirect information on articular soft tissues structures can be present in case of calcification within these structures, mostly a sign of degeneration

but can also sometimes be an incidental finding. Also using stress radiographs, an indirect evidence of articular ligament rupture, can be obtained.

CT provides additional useful information in all processes where avulsions or fragmentation are involved. These disorders are not always visible on radiographs. CT proved to be extremely useful in the detection of avulsion fractures of intra-articular ligaments like the cranial cruciate ligament and the tendons of the extensor digitorum longus and the popliteus muscles (Figures 3,4). In this case, CT confirmed the diagnosis. Compared to radiography, the use of CT could detect many more intra-articular fragments, which provides important information to the surgeon, especially when arthroscopic treatment is envisaged. The intra-articular administration of iodinated contrast medium (computed tomographic arthrography) enables the identification of several ligamentous structures within the hip joint. Degenerative changes can be identified in an earlier stage than on conventional radiographs. In cases where treatment of bone tumours is considered, CT enables a more exact demarcation of the affected tissues and helps to decide to what extent the tumour has to be excised. In such cases, CT guided biopsies can be accurately obtained.

V. Conclusion

The current study concluded that:Histopathology, Radiography and Computed Tomography each of them has a diagnostic value in diagnoses of canine osteo-Arthritis, Althoughconventional radiography is the most common method used to evaluate osteoarthritis.

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Establishment of Reference Values for Renal Length and Volume for Normal Adult Sudanese using M RI Disc Summation Method

By Mazin Babikir Abdullah, Mohammad Elfadil Mohamed Garelnabi, Caroline Edward Ayad & Elsafi Ahmed Abdalla
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Abstract- Knowledge of kidney character is important for clinical assessments of renal diseases. The aims of this study were to establish a normal range of values for kidney length and volume in normal Sudanese adults with no known history of renal disease and to determine the usefulness of body mass index (BMI), Body surface area (BSA), Glomerular filtration rate (GFR), Total body water (TBW), Creatinine Clearance(Crcl), Serum Creatinine Level(Scr) for prediction of kidney characters.

98 consecutive patients (43 females; 55 males) who had undergone axial T1, T2 weighted abdominal MRI images, were obtained during the period from June 2012 to June 2013 for indications other than renal diseases. Excluded patients were those who had renal cysts, hydronephrosis, and congenital kidney diseases. Detailed demographic information of the sample wererecorded. The kidneys volume and length were measured using Disc Summation Method and the relations between the variables were studied.

Keywords: MRI; disc summation; kidney measurements; volume.

GJMR-D Classification : NLMC Code: WJ 302

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The study showed that the kidneys length measured for normal Sudanese subjects were 10.08±0.46, 10.67±0.47 and the volumes were 101.6±12.98, 104.0±12.99 for right and left kidneys respectively, and it differed from other population. There were significant differences between males and females measurements and the correlation was significant between kidneys length and volume with BMI, TBW and subjects height. New equations were established to measure the kidneys length and volume.

Our study confirmed that there was significant relation between the CrCl, GFR, and serum creatinine level with BSA, BMI, TBW, weight, gender and age and revealed that the kidney volume predicted the renal function significantly at p=0.005, for SCr *p-value*=0.056, 0.007, CrCl *p-value*=0.054, 0.043 and GFR *p value*= 0.051, 0.59 for right and left kidneys volume.

MRI measurements using disc summation method for renal volume and length were accurate and a reference values were established for adult Sudanese subjects and were well correlated with body parameters and renal function.

Keywords: MRI; disc summation; kidney measurements; volume.

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I. Introduction

Renal length and volume are important parameters in clinical settings.[1-5] Kidney volume is a more sensitive index of kidney size than kidney length for the detection of renal abnormalities.[6] It is also excellent predictor of renal function and correlates very well with body indices.[7]

A number of investigators have reported reference values for renal length [8-13] and renal volume in healthy adults [8-9], as measured by ultrasonography. The ultrasonography method that is used to measure kidney volumes is two-dimensional in nature, and is operator dependent, and uses geometric assumptions about the shape of the kidney to estimate kidney volumes. In contrast, computed tomography (CT) and magnetic resonance imaging (MRI) can acquire three-dimensional data and, therefore, it can estimate organs volumes. In the case of CT, the need for ionizing radiation and contrast media limits its place as a routine noninvasive imaging method for measuring kidney volumes. Conversely, MRI has the benefit of acquiring true tomographic data along any direction, without the constraints of ionizing radiation and nephrotoxic contrast burden. Nevertheless, the literature contains few reports of renal dimensions as determined by MRI.[9] Furthermore, although CT and MRI can be used to measure renal volume accurately with voxel count–based methods [14]. These techniques present problems of radiation exposure, and toxicity associated with renal contrast agents [15]. MRI estimation of kidney volumes can be determined using different methods including the water displacement, disc-summation and other mathematical methods[16].It should be noted that tomographic images of the kidneys that were acquired using MRI can provide reliable and consistent determinations of kidney volume without the geometric assumption limitations that are inherent in other methods of measurements.[16].The changes in the acquired spatial resolution of the imaging techniques from a coarse spatial resolution to a fine spatial resolution did not have an appreciable effect on the mean kidney volume measured. This suggests that the spatial resolution that was used in routine patient studies is sufficient to

measure the kidney volumes accurately, and does not introduce significant errors in volume calculations. [16]
A number of reports have depicted measurement of renal length and volume in the healthy Western population, but there are limited data regarding MR measurement of renal dimensions in adults and as far as our knowledge no study was done regarding the adult Sudanese's kidneys measurements in the open literature as an African population.

The purpose of this work was to establish reference values for renal length and volume using MRI disc summation method in normal Sudanese adults with no clinical history of renal disease as well as to correlate the measurements with body characteristics including body mass index (BMI), Body surface area (BSA), Total body water (TBW), and renal function including Creatinine Clearance (Crcl), Serum Creatinine Level (Scr) and Glomerular filtration rate (GFR),

II. Materials and Methods

a) Sample Selection and Technique used

98 consecutive patients (43 females; 55 males) their ages were between 20-45 years who had undergone axial T_1, T_2 abdominal MRI weighted images were obtained between June 2012 and June 2013 for indications other than renal diseases. Excluded patients were those who had renal cysts, hydronephrosis, and congenital kidney diseases. Detailed demographic information of the population including age, gender, weight, length, BMI, BSA, Total body water, Serum Ceriatinine clearance, GFR was recorded.

MRI machine 1.5 Tesla was used at Alamal Hospital, the selected Sequences were Scout: axial, sagittal, and coronal .Sequence 1and 2 were coronal and axial T_2-weighted: TSE, breath hold: TR = 3000–4000,TE = 90–140.TSE, respiratory triggering TR = 1900–2300,TE = 100,Flip angle 90°STIR:TR = 2200, TE = 60, TI = 100 HASTE, breath hold: TR = 11.9, TE = 95,Slice thickness: 4–6mm— Slice gap: (0.8–1.2mm),Phase encoding gradient: LR,FOV: 380–400mm, Sequence 3 was axialT_1-weighted, GRE (FFE), breath hold:TR = 120–140,TE = 4 Flip angle 60°GRE (FFE), respiratory compensation: TR = 500–600, TE = 10or as SPIR: TR = 500–600,TE = 15,orTSE, breath hold: TR = 320, TE = 14, Matrix = 140 × 256.

b) Method of Kidneys length and volume measurements

Disk summation method (DSM) was used to calculate the volume of normal kidney in normal individuals. In the DSM, the measurement is dependent on the picture element (pixel-px), by counting the total number of pxs per unit area (only renal area excluding the rest of FOV, and is represented in (px^2). Then the pixels were converted into units of area in (mm^2). That was done by multiplying the area in (px^2) by conversion constant (0.26^2), Then multiplying the product by slice thickness in (mm), which represents slice height an Z-axis ,and consequently the product is in unit volume (mm^3) for the single slice. Then dividing the value in (mm^3) over (1000) to convert to (cm^3).

This formula was applied to each separate slice to final the total volume of both kidneys. As shown in following equations:

- Px^2(number of pixels)^{2}x$(0.26)^2$=Area in $(mm)^2$
- Area $(mm)^2$xslice thickness (mm) = volume $(mm)^3$
- Volume $(mm)^3/1000$ = volume $(cm)^3$
- Total volume of kidney = ∑slices volumes.

Three measurements were calculated to determine the (complete volume) including length, width, and depth, according to the assumption that kidney is degrader (cylindrical shape), which was the product of multiplying 3 dimension length Z-axis x width X-axis x depth Y-axis. To determine the length which is represented by unit distance in the Z-axis according to patient's position inside the gantry of MRI, and can be expressed by slice thickness, and is calculated by:

- Length = number of slices (in which kidney appeared) x slice thickness (cm).
- The width was also represented in unit length in the X-axis, and calculated by the cube root of volume $(cm)^3$.
- Width = $\sqrt[3]{totalvolume\ (cm)^3}$.
- The depth, in unit length on the Y-axis was calculated by, dividing the square root largest area calculated in $(mm)^2$ over 10.
- Depth (cm) = $\sqrt{largest\ area\ (mm)^2}/10$.
- After determining the 3 dimensions above, the assumed renal volume can be calculated based on the mathematical rule:
- Volume $(cm)^3$= length x depth x width.

c) Methods of variables evaluation

Variables including: height; which was measured in (cm). weight in (kg), age in (yrs) and gender (male or female) were evaluated. For measuring dependent variables: Body surface area (BSA) was measured in $(mm)^2$, total body water (TBW) in (liters) and Glomerulo filtration rate (GFR) by (Cock –Craft-Gault) (CG) equation in (ml/min/1.73.mm^2).

To calculate BSA in $(m)^2$:{(height (cm))x(weight(kg))x3600}x1/2

Total body water is calculated by Watson's formula:

- TBW_{male} = (2.477-0.09516 x age (yrs) +0.1074 x height (cm) +0.3362 x weight (Kg).
- TBW_{female} = (-2.097+ (0.106) x height (cm) +0.2466 x weight (kg).
- To determine (GFR), the CG-GFR equation was used:

- CrCl X BSA / 1.73(m)^2=GFR .
- Ceriatinine clearance (CrCl) = (140-age) x weight (kg) x {0.85 if female}/72Xserum Ceriatinine.
- Serum Ceriatinine in Sudanese population= (BMI*0.031) + (age*0.003) + (Gender*-0.52).

III. Results

Table 1 : Descriptive statistics of the Normal Sudanese Body Characteristics (Total Sample)

	Descriptive Statistics			
	Minimum	Maximum	Mean	Std. Deviation
Weight	66.00	101.00	83.40	8.21
Age	20.00	45.00	32.38	6.06
Body surface area(BSA)	1.55	2.50	2.04	0.20
Body Mass Index(BMI)	21.10	34.95	26.81	3.20
Height	164.00	186.00	176.0	4.49
Total body water (TBW)	33.20	52.64	42.76	5.49
Serum Creatinine	0.67	1.15	0.8	0.10
Creatinine Clearance	62.62	161.51	99.36	21.76
Glomerular filtration rate(GFR)	56.07	222.64	119.0	37.08

Table 2 : Descriptive Statistics Mean, Standard deviation of Kidneys volume, and length for the total sample

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Right Kidney Volume(Cm^3)	98	80.32	122.91	101.6	12.98
Right Kidney Length.(Cm)	98	9.00	11.25	10.18	0.46
Left Kidney Volume (Cm^3)	98	82.56	126.54	104.0	12.99
Left Kidney Length(Cm)	98	9.00	11.70	10.67	0.47

Table 3 : Descriptive Statistics Mean, Standard deviation of the variables for (55)Males

	Descriptive Statistics			
	Minimum	Maximum	Mean	Std. Deviation
RT Kidney- volume	80.32	122.91	105.0	13.00
RT kidney length	9.00	11.25	10.2	0.48
LT Kidney volume	82.56	126.54	108.0	12.89
LT kidney length	9.90	11.70	10.71	0.46
Weight	72.00	101.00	83.45	7.54
Age	21.00	40.00	31.49	4.82
Body Surface area(BSAm^2)	1.79	2.50	2.07	0.18
Total Body Water(TBW)	34.89	52.64	46.10	3.70
Body Mass Index(BMI)	21.10	34.95	26.16	2.77
Serum Creatinine	0.69	1.15	0.85	0.09
Creatinine Clearance	65.61	161.51	106.0	20.96
CG-GFR	71.52	222.64	130.0	36.99
Height	169.00	186.00	178.0	3.92

Table 4 : Descriptive Statistics Mean, Standard deviation of the variables for (43)females

	Descriptive Statistics			
	Minimum	Maximum	Mean	Std. Deviation
RT Kidney- Volume	80.43	121.12	96.15	10.84
RT Kidney Length	9.00	11.25	10.14	0.44
LT Kidney Volume	83.29	122.49	98.81	11.10
LT Kidney Length	9.00	11.25	10.63	0.50
Weight	66.00	100.00	83.34	9.08
Age	20.00	45.00	33.53	7.25
Body Surface area(BSAm^2)	1.55	2.43	2.01	0.21
Total Body Water(TBW)	33.20	52.64	38.49	4.34

Body Mass Index(BMI)	22.41	34.95	27.64	3.53
Serum Creatinine	0.67	1.11	0.85	0.12
Creatinine Clearance	62.62	124.91	89.64	18.87
CG-GFR	56.07	172.46	1.06	33.16
Height	164.00	182.00	1.73	3.63

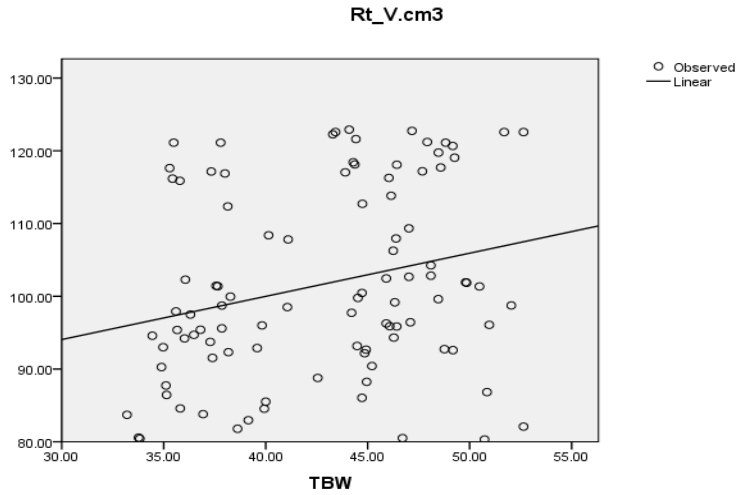

Figure 1 : Scatter plot diagram showed the linear relationship between the total body water (TBW) and RT kidney volume and the correlation is significant (0.013) at *p* value 0.005. RT Kidney Volume=0.593TBW+76.25 R^2=0.063

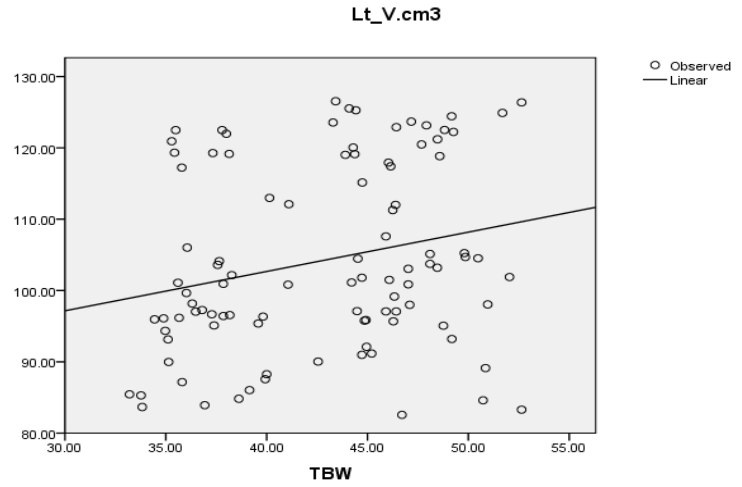

Figure 2 : Scatter plot diagram showed the linear relationship between the total boy water (TBW)and LT kidney volume and the correlation is significant(0.021) at p value 0.005. Left Kidney Volume=0.551TBW+80.61 R^2=0.054

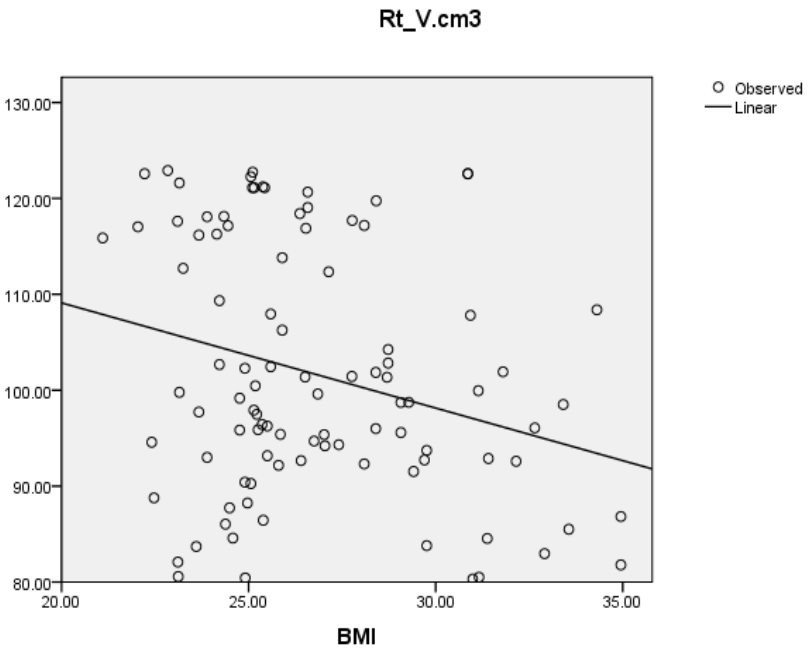

Figure 3 : Scatter plot diagram showed the linear relationship between the body mass index(BMI) and RT kidney volume and the correlation is significant(0.007) at p value 0.005 Rt kidney volume=1.096BMI+131.0 $R^2 = 0.073$

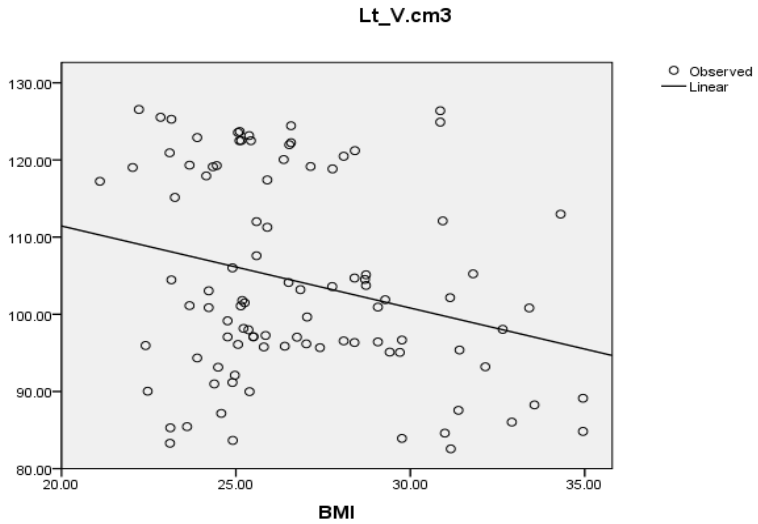

Figure 4 : Scatter plot diagram showed the linear relationship between the body mass index(BMI) and LT kidney volume and the correlation is significant(0.009) at p value 0.005. LT kidney volume =1.062x+132.6 R^2=0.068

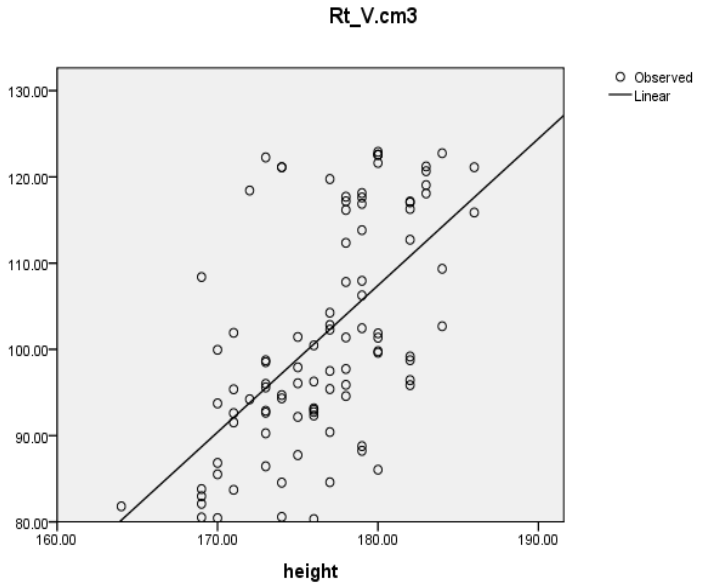

Figure 5 : Scatter plot diagram showed the linear relationship between the Height and RT kidney volume and the correlation is significant (0.000) at p value 0.005 RT kidney volume =1.702xHeight+198.9 R^2=0.347

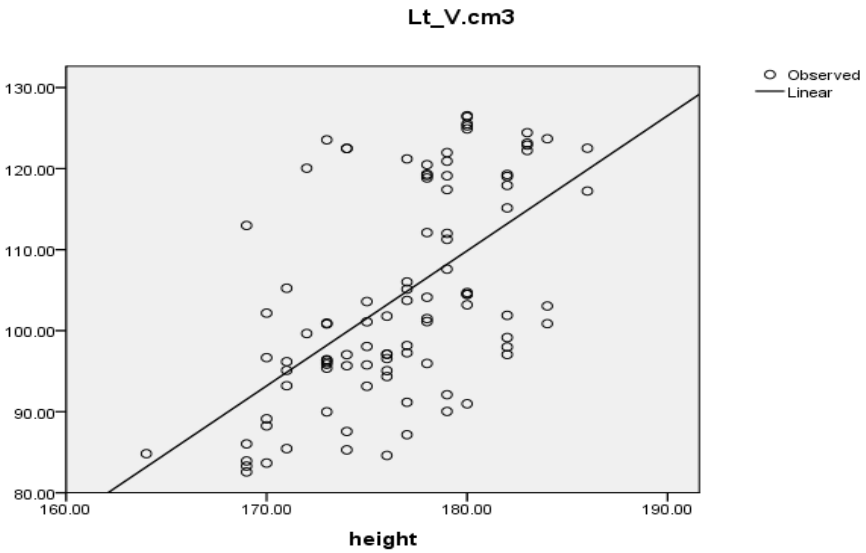

Figure 6 : Scatter plot diagram showed the linear relationship between the Height and LT kidney volume and the correlation is significant(0.000) at p value 0.005 Left kidney volume=1.667xHeight+190.2 R^2=0.332

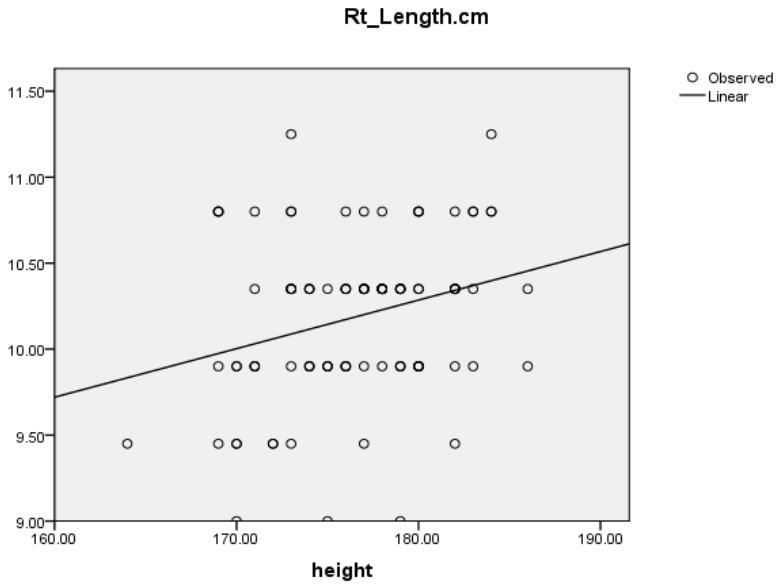

Figure 7 : Scatter plot diagram showed the linear relationship between the Height and RT kidney Length and the correlation is significant(0.007) at p value 0.005 RT kidney length =0.028Height+5.202 R^2=0.073

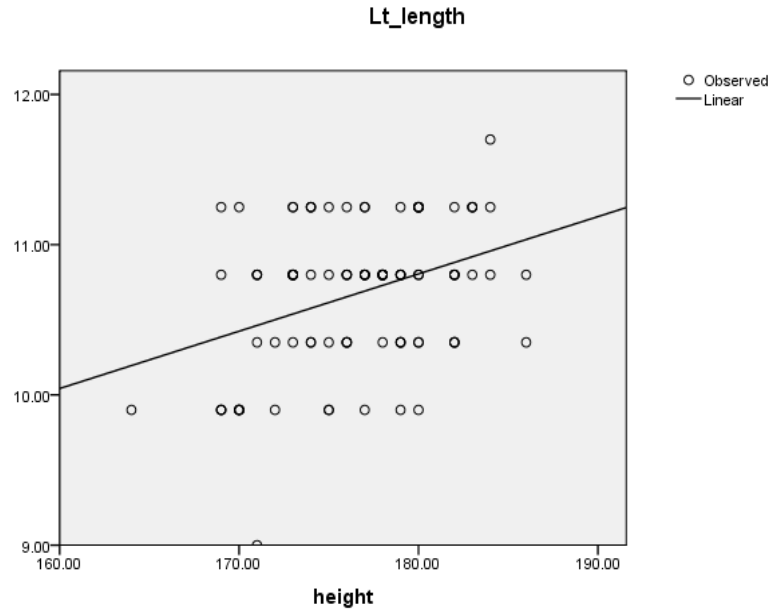

Figure 8 : Scatter plot diagram showed the linear relationship between the Height and LT kidney length and the correlation is significant(0.000) at *p* value 0.005 LT kidney length =0.038Height+3.940 R^2=0.128

IV. Discussion

Renal length and volume measurements are clinically relevant, serving as surrogates for renal functional reserve, and are used frequently as the basis for making clinical decisions. Serial measurements also can provide information regarding disease progression or stability.

The aims of this study were to establish reference values and define the normal kidney length and volume of Sudanese adults using MRI as well as to determine the relationship between kidney character and Sudanese body indices.

Correlations between measurements of the kidneys and body indices were calculated. The data were expressed as means ± SD. Kidneys length and volume were analyzed separately for males and females as well as the total sample. The data statistical analyses were performed using Excel software programme and statistical analyses were performed using the independent sample t-test, simple correlations (SPSS software version 16.0 USA). Statistical significance was assumed at $P < 0.05$.

Table [1] showed the demographic data of the whole sample including weight, age, body surface area (BSA), body mass index (BMI), height, total body water

(TBW), serum Creatinin, creatinin clearance , Glomerular filtration rate (GFR). The kidneys volumes and lengths for the total sample were measured and also for males and females subjects as presented in tables [2] and[4,5] The kidneys volumes were found to be in the ranges from (80.32-122.91) with mean=101.6±12.98 and (82.56-126.54) with mean=104.0±12.99 for the right and left kidneys. The males' kidney volume exceeded the volume of females by (1.79 and 4.09) for right and left kidneys. Right and Left Kidney volume have significant relation p=0.000with gender. the measurements of kidneys volume differs from other population[17-21.]

The cause of this difference may be due to the method of measurements or other factors. In the literature it was noted that the Sonographic measurements of renal volume are very inaccurate [9,22,23] The volume of kidneys can be accurately measured by CT scanning with errors of 3% or less [24] However, studies to date have measured total kidney volume, which includes tissue that does not contribute to renal function. The justification that the male has greater kidney volume than female is that The occurrence of larger glomeruli in men is solely dependent on their greater body surface area than females [25]. The effect of gender on renal character may be due to a direct action of sex steroids on kidney growth or is secondary to differences in body composition, or other factors [26]. Measuring body mass index has shown enhanced correlation with adult renal volume (p=0.007,0.009) for right and left renal volume than body surface area (p=0.207,209). This agreed with the study done in children and adults [26] Right and Left kidney volume correlates more strongly with body size than with age (p=.544, .575) this also consigned to the study findings done in children [26] This, together with the fact that BSA are closely linked in adults, suggests that renal enlargement during development is an adaptation to body size and that this continues into adulthood.[27]

Renal length determination is common in everyday radiology practice. However, a normal range of kidney sizes may not apply to people of all body habitus. This study investigates this relationship in order to determine normal ranges in relation to body habitus

Kidney lengths were measured the patients had normal serum creatinine levels, ceratinen clearance with no history of renal disease, no renal masses, and normal-appearing kidneys on MR T_1 weighted images. The patients information were recorded. The mean renal length was 10.18±0.46, 10.67±0.47 for Right and left kidneys respectively .Males have mean length 10.23±0.49 and 10.7±0.46 and females have mean kidneys length =10.14±0.44, 10.6±0.5 for Right and left kidney length correspondingly. Statistical analysis demonstrated a relationship between kidney length and body weight and height, BMI, BSA, CrCl, GFR. A significant relation was found between the kidney length and body height. Additionally, kidneys lengths were generally larger in males than females, that means normal renal length varies according to patients' body habitus. This variation can be expressed as a function of body height, which can be represented by an equation and used as an easy reference in clinical practice.

Left kidney length=0.038height+3.940 R^2=0.128

Right kidney length=0.028height+5.202 R^2 =0.073

Both kidney volumes and kidney lengths were significantly correlated to body indices (BMI, height, TBW) at p value=0.013, 0.021 for TBW with RT and left kidney volume and 0.007,0.009 the BMI with RT and left volume,0.000,0.000 the height with right and left volume and then0.007,0.000the height with right and left kidney length [figures 1-8] an equations were established to predict the kidneys length and volume when the Sudanese BMI,TBW, Height are well known. We also evaluated the predictability of kidney volume and kidney length to renal function, by using the CG equation which is regarded as accurate and less biased equation to estimate GFR in healthy adults [27, 28]

Our study showed that there was significant relation between the CrCl, GFR,serum creatinen level with weight, BSA,BMI, age TBW, gender. The result revealed that the kidney volume predicted the renal function significantly SCr 0.056, 0.007, CrCl 0.054, 0.043, GFR 0.051, 0.59 for right and left kidneys volumes whereas the kidney length did not.

The study concluded that MRI measurements using disc summation method for renal volume and length is an accurate method and the renal length and volume for Sudanese subjects were different from other population and between males and females .Renal volume can predict the renal function significantly. Body habitus has an impact in kidney length. Equations to predict Sudanese renal length and volume were built up and reference values were established.

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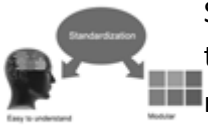

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3. Submission of Manuscripts,

4. Manuscript's Category,

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12. Make all efforts: Make all efforts to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in introduction, that what is the need of a particular research paper. Polish your work by good skill of writing and always give an evaluator, what he wants.

13. Have backups: When you are going to do any important thing like making research paper, you should always have backup copies of it either in your computer or in paper. This will help you to not to lose any of your important.

14. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several and unnecessary diagrams will degrade the quality of your paper by creating "hotchpotch." So always, try to make and include those diagrams, which are made by your own to improve readability and understandability of your paper.

15. Use of direct quotes: When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

16. Use proper verb tense: Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

17. Never use online paper: If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

18. Pick a good study spot: To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

19. Know what you know: Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

20. Use good quality grammar: Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straight forward. put together a neat summary.

21. Arrangement of information: Each section of the main body should start with an opening sentence and there should be a changeover at the end of the section. Give only valid and powerful arguments to your topic. You may also maintain your arguments with records.

22. Never start in last minute: Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

23. Multitasking in research is not good: Doing several things at the same time proves bad habit in case of research activity. Research is an area, where everything has a particular time slot. Divide your research work in parts and do particular part in particular time slot.

24. Never copy others' work: Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

25. Take proper rest and food: No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

26. Go for seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

27. Refresh your mind after intervals: Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

28. Make colleagues: Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

29. Think technically: Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

30. Think and then print: When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

31. Adding unnecessary information: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

32. Never oversimplify everything: To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

33. Report concluded results: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.

Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

· Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

· Keep on paying attention on the research topic of the paper

· Use paragraphs to split each significant point (excluding for the abstract)

· Align the primary line of each section

· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

· Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives

· Shun use of extra pictures - include only those figures essential to presenting results

Title Page:

Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.

Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

Introduction:

The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

Procedures (Methods and Materials):

This part is supposed to be the easiest to carve if you have good skills. A sound written Procedures segment allows a capable scientist to replacement your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt for the least amount of information that would permit another capable scientist to spare your outcome but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section. When a technique is used that has been well described in another object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text all particular resources and broad procedures, so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step by step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a argument should be. Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly described. Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved with prospect, and let it drop at that.

- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.

Administration Rules Listed Before Submitting Your Research Paper to Global Journals Inc. (US)

Please carefully note down following rules and regulation before submitting your Research Paper to Global Journals Inc. (US):

Segment Draft and Final Research Paper: You have to strictly follow the template of research paper. If it is not done your paper may get rejected.

- The **major constraint** is that you must independently make all content, tables, graphs, and facts that are offered in the paper. You must write each part of the paper wholly on your own. The Peer-reviewers need to identify your own perceptive of the concepts in your own terms. NEVER extract straight from any foundation, and never rephrase someone else's analysis.

- Do not give permission to anyone else to "PROOFREAD" your manuscript.

- Methods to avoid Plagiarism is applied by us on every paper, if found guilty, you will be blacklisted by all of our collaborated research groups, your institution will be informed for this and strict legal actions will be taken immediately.)
- To guard yourself and others from possible illegal use please do not permit anyone right to use to your paper and files.

Criterion for Grading a Research Paper (Compilation) by Global Journals Inc. (US)

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals Inc. (US).

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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