Platelet aggregation defects in women with endometriosis

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PLATELET AGGREGATION DEFECTS IN WOMEN WITH ENDOMETRIOSIS

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Abbreviations

BDs	Bleeding Disorders
vWF	von Willebrand Factor
VWD	von Willebrand Disease
PFDs	Platelet Function Disorders
GP	Glycoprotein
BSS	Bernard-Soulier Syndrome
GT	Glanzmann Thrombasthenia
HMB	Heavy Menstrual Bleeding
PBAC	Pictorial Blood Assessment Chart
TF	Tissue Factor
iNO	Inducible Nitrous Oxide
NK-Cells	Natural Killer Cells
COX-2	Cyclooxygenase-2
IBD	Inherited Bleeding Disorders
PIQ-6	Pain Impact Questionnaire-6
rASRM	Revised American Society For Reproductive Medicine
ECM	Extracellular Matrix
LTA	Light Transmission Aggregation
TEGPM	Thromboelastometry Platelet Mapping
DDAVP	1 – deamino–8-D-arginine vasopressin

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Abstract

Title: PLATELET AGGREGATION DEFECTS IN WOMEN WITH ENDOMETRIOSIS

Keywords: Platelet aggregation, Endometriosis, bleeding disorders, platelet function disorder, von Willebrand factor

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Major progress has been seen in the past few decades in the management of gynecological conditions and obstetric care in women with bleeding disorders (BDs). However, there remain many ambiguous issues within the field. A sequence of observational studies was conducted to address these issues with a goal to improve patient care. In the recent findings showing that platelets play important roles in the development of endometriosis. Hence, this review was undertaken to see if there was a connection between bleeding disorders specially platelet aggregation defect and endometriosis. This association was explored in animal models as well as in clinical studies suggesting that women with endometriosis have a higher rate of platelet aggregation defect. Deficiency of von Willebrand factor (VWF), a protein required for the normal adhesion of platelets to the site of injured endothelium may be associated with advanced stage of endometriosis on laparoscopy. The present review concludes that platelets may be a culprit in the development of endometriosis and that platelet aggregation were seen in endometriotic lesions.

SAŽETAK

Naslov: POREMEĆAJI AGREGACIJE TROMBOCITA U ŽENA SA ENDOMETRIOZOM

Ključne riječi: agregacija trombocita, endometrioza, poremećaji krvarenja, poremećaji trombocita VonWillebrand faktor

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Posljednjih nekoliko desetljeća bilježimo veliki napredak u liječenju ginekoloških poremećaja i opstetričke skrbi u žena sa poremećajima koagulacije. Unatoč tome ostaje niz nerazriješenih pitanja u ovom području. Niz opservacijskih studija provedeno je radi rasvjetljavanja ove problematike s glavnim ciljem poboljšanja skrbi o bolesnicama. Nedavne studije pokazale su da trombociti igraju važnu ulogu u razvoju endometrioze. Cilj ovog preglednog rada bio je istražiti postoji li povezanost između između poremećaja koagulacije, posebice poremećaja agregacije trombocita i endometrioze. Ova je povezanost istraživana na životinjskim modelima kao i u kliničkim studijama koje ukazuju da žene s endometriozom imaju veću učestalost poremećaja agregacije trombocita. Manjak von Willebrandovog faktora (vWF), proteina potrebnog za normalno prianjanje trombocita na mjesto ozlijeđenog endotela, povezan je s višim stupnjem endometrioze dijagnosticiranim laparoskopski. Zaključak ovog preglednog rada je da trombociti mogu biti odgovorni za razvoj endometrioze odnosno da je poremećaj u agregaciji trombocita nađen u endometriotskim lezijama.

1. Introduction

Endometriosis, a long term benign inflammatory condition that is characterized by the presence of functional endometrial like tissues outside the uterine cavity. A number of publications have shown the role of platelets in the development of endometriosis. Consequently, the exact mechanism is still an enigma. However, research has suggested that there may be a link between endometriosis and platelet aggregation defects. The sole purpose of this thesis is to provide a structured background review focusing on the correlation seen between endometriosis and bleeding disorders, primarily in platelet aggregation defects. The present review will tackle the unresolved issues that have not been addressed previously. The series of studies included in this thesis are presented to address these issues and provide better evidence to optimize patient care.

2. Methods

A literature search was conducted to review publications from the early 70's to present. Online sources of medical databases included PubMed, New England Journal of Medicine and Various reading materials. The search was conducted with combination of terms that included “bleeding disorders”, ”vWF,” “endometrisois,” “platelet aggregation defect,” “heavy menstrual bleeding” and others that were assumed to be relevant.

3. Bleeding disorders

Bleeding disorders (BDs) are a group of conditions that result from a deficiency or abnormal functioning of coagulation factors or proteins. Bleeding disorders in women are more common than was suspected previously. This is due to an increase in number of studies and publications that have reported morbidity in women with bleeding disorder in recent years (1- 3).

Women with bleeding disorders are at risk of excessive bleeding during their periods, childbirth and after any surgical intervention. Increased awareness among obstetricians and gynecologists, close collaboration with the local centers for bleeding disorders and availability of management guidelines are essential to minimize these risks.

3.1. Von Willebrand Disease

Among all BDs, Von Willebrand Disease (VWD) seems to be the most common bleeding disorder with higher prevalence in women. Many epidemiological studies have shown that up to 1% of the general population has the condition (4). Originally described by the Finish physician Erik von Willebrand in 1926 (5). VWD is characterized by the quantitative deficiencies and/or qualitative defects in von Willebrand factor (VWF), a large adhesive glycoprotein synthesized by vascular endothelial cells. VWF plays an important role in primary hemostasis by promoting the tethering and adhesion of circulating platelets as well as platelet aggregation at the site of injury to prevent blood loss (6). It binds to and stabilises the procoagulant factor VIII (FVIII) in plasma, thus indirectly contributing to the generation of fibrin (7). A slight variation in VWF levels among women result from ABO blood group, ethnicity, and phases of the menstrual cycle (8). VWF levels increase during

pregnancy, with the use of combined oral contraceptives and are elevated in the neonatal period (9, 10).

3.2. Platelet function disorders

Platelet function disorders (PFDs), a heterogeneous group of congenital bleeding diatheses, fall into the categories of either platelet function defects or structure. How common platelet function disorders (PFDs) are among general population has not been assessed properly. Fortunately, severe cases are rare and are usually diagnosed in childhood due to the severity of the bleeding symptoms.

PFDs are distinguished by quantitative or functional defects of platelet adhesion, receptors, secretion, enzymes, and dysfunction in downstream signalling pathways (11). The most common deficiencies are of glycoprotein (GP) mediators of adhesion (Bernard-Soulier syndrome (BSS)) and platelet aggregation (Glanzmann thrombasthenia (GT)). Deficiency of the GPIb/V/IX complex associated macrothrombocytopaenia and haemorrhagic due to mutations in GPIBA, GPIBB, GP9 genes can give rise to BSS (12). Partly missing or completely absent expression of the integrin GPIIb/IIIa (α-IIb/β-3) or qualitative defects of the receptor due to mutations in either ITGA2B or ITGB3 genes result in the disorder of platelet aggregation, GT (13). Several defects of other platelet receptors (GPVI, TP, P2Y12) associated with a bleeding diathesis have been identified (14).

3.3. Bleeding disorders and heavy menstrual bleeding

Heavy Menstrual Bleeding (HMB) is the most common bleeding symptom in women with BDs. HMB is seen in 78-97% of women with von Willebrand disease (15). In a case control study, 66 women with VWD were

assessed for menstrual blood loss using PBAC score. Women with VWD had significantly increased menstrual blood loss (PBAC score > 100) (p = 0.001) compared to 69 women without VWD. They also showed increased menstrual flooding and longer duration of menses (15). Furthermore, a history of anemia and reduced quality of life during menstruation were also observed in women with VWD (16). Platelet function disorder (PFD) has been linked to HMB in women in about 50- 98% of cases. This is usually dependent on the underlying disorder BSS and GT. Mild defects in PFDs are usually underestimated in women with HMB. Specialized tools and experienced individuals are required to diagnose these disorders. In women with HMB, PFDs have been observed to be more common than VWD (17). A multi study that was carried out in the US included 232 women with HMB and a PBAC score > 100. A defect in hemostasis was detected in 73.3% of the women. The frequency of platelet aggregation defects among women with HMB was 51.5%, which was significantly higher (17.3%) than the control group (18).

4. Endometriosis

Endometriosis, a condition characterized by the presence of endometrial glands and stroma in areas outside the uterus, is an estrogen-dependent, benign inflammatory disorder and a major contributor to pelvic pain and subfertility (19). It is very challenging to determine the exact prevalence, partially due to the variability in clinical presentation, and partially due to the fact that surgical visualization of endometriotic implants is regarded as the gold standard for a definitive diagnosis (19). It is estimated to affect 6%–15% of reproductive-aged women in hospital-based studies (20), with a peak between 25 and 35 years of age. Endometriotic implants are usually located within the pelvis but

may also be found in other locations such as the ovaries, ovarian fossa, pelvic peritoneum, rectovaginal septum, uterosacral ligaments, and cul-de sac.

4.1 Pathogenesis of endometriosis

The exact pathogenesis of endometriosis still remains unclear. It is sustained by theories from long ago and the most common accepted hypothesis is the retrograde menstruation theory; viable menstrual mix of blood and endometrial tissue shredded during menstruation passing to the abdominal cavity through the Fallopian tubes, due to a pressure gradient originating dysynergic uterine contractions (21). Over time, the endometrial cells adhere to the peritoneal surfaces, proliferate, grow and invade pelvic structures. The amount, duration and frequency of pelvic exposure to regurgitated endometrium may also determine the severity of endometriosis (19). The risk of developing endometriosis is higher in women with a prolonged menses of more than 6 days (22).

Immunological mechanisms are also implicated in the pathogenesis of endometriosis suggesting that there is evidence that endometriosis is, in fact, a pelvic inflammatory condition. The peritoneal fluid has an increased concentration of activated circulating monocytes, macrophages and release of inflammatory cytokines that stimulate ectopic endometrial cell proliferation (23).

"Celomic metaplasia involves the transformation of normal peritoneal tissue to ectopic endometrial tissue" is another suggested theory. Endocrine-disrupting chemicals might also play an important role in such transformation of peritoneal mesothelium. Over the past few decades, a lot of research effort has been put into pathogenesis of endometriosis. The genetics and molecular make of the ectopic and eutopic cells have been very well studied and the results of genome-wide association studies are consistent with a heritable component in endometriosis (24). Women with endometriosis report heavier menstrual

bleeding compared to controls and it is known that a significant proportion of patients with menorrhagia may have bleeding disorders (46). Patients with endometriosis also reported easy bruising and mucosal bleeding. One hallmark of endometriosis is the recurrent or cyclical heavy bleeding, which is indicative of vascular injury that requires wound healing or tissue repair.

4.2. Endometriosis symptoms

The most common presenting symptom of endometriosis is pelvic pain. The pain is usually cyclical and can occur with lower back pain. Endometriosis can also result in dysmenorrhea, dyspareunia, dyschezia and dysuria. Rarely endometriosis results in abnormal rectal bleeding or hemoptysis (25). A study demonstrated that 25% of 5540 women with endometriosis reported dysmenorrhea to their general practitioner three years prior to diagnosis, 24% reported urinary tract symptoms, 11% reported pain during sexual intercourse, and a small percentage reported rectal bleeding or dyschezia (20). The number of women being asymptomatic is difficult to determine. A well-described paradox of endometriosis is that severity of disease seen at laparoscopy staging does not correlate well with severity of symptoms, and the reason for this is unclear. Infertility is a common symptom of endometriosis. Some people only find out that they have the condition when they experience difficulty getting pregnant. An estimated 25-50% of women with infertility have endometriosis, and around 30-50% of women with endometriosis have infertility (26). How endometriosis affect fertility is still unclear, but it is thought to be due adhesion of endometrial tissues that alter tubal patency, reduced ovarian reserve with endometrioma formation, altered embryo transport and impaired implantation due to proinflammatory environment.

The chronicity of the condition can have a profound impact on women's lives including associated heavy bleeding, pain, infertility, reduced ability to carry out normal everyday activities, loss in earned income, social withdrawal, psychological disorders and sexual relationships. A prospective, multi-centre European study estimated the average annual total cost per patient with endometriosis was €10,000 including cost of healthcare, and loss of productivity (27).

5. Platelet aggregation defects and endometriosis

There is not a lot of existing evidence to support the relation between the prevalence of endometriosis in women with platelet dysfunction. Recent years findings show that platelets play an important role in the development of endometriosis. Endometriotic lesions undergo cyclic and repeated bleedings that signify tissue injury and subsequent repair (28). This suggests that platelets must be involved in the development of endometriosis.

5.1. Platelet aggregation defects and endometriosis in animal models

In-vitro experiments, and animal models has been shown that platelets can promote angiogenesis and cellular proliferation (29) by secreting angiogenic factors such as VEGF. The study examined platelets aggregation in tissues from 58 women with endometriosis and 47 without (29). Local factors within the endometrial tissue play an important role in promoting pro-hemorrhagic environment. Menstruation occurs following progesterone withdrawal, causing downregulation of tissue factor (TF) and plasminogen-activator inhibitor 1 (PAI-1). Inducible nitrous oxide (iNO) inhibits platelet aggregation that leads to relaxation of smooth muscles and vasodilation

resulting in increased menstrual blood flow (30). Hormonal fluctuations around the time of menstruation may impair both systemic and local primary hemostasis. Impaired hemostasis leads to increased menstrual blood flow and prolonged duration of menses, both of which may exacerbate endometriosis, according to the retrograde menstruation/implantation theory (31).

Experiments on mice with induced endometriosis in which platelets, NK cells or both were depleted showed platelets are responsible for NK cell cytotoxicity in endometriosis. Platelet depletion resulted in significantly reduced lesion weight in mice with induced endometriosis due to reduction of inflammatory mediators such as Cyclooxygenase- 2 (COX2) and vascular endothelial growth factor (32). *In- vivo* study of anti-platelet treatment in mice with surgically induced endometriosis showed a significant reduction in ectopic lesion area (33).

5.2. Association between platelet dysfunction, HMB and endometriosis

The prevalence of HMB has been shown to be as high as 51% in BSS and up to 98% in women with GT (34). Several studies aimed to detect impaired hemostasis among women with HMB and platelet dysfunction. In a study among 232 women of reproductive age with HMB a platelet ATP release abnormality was found in 58.9% (35). A prospective cohort study showed that 47% of 175 women with HMB had platelet function disorder compared to 0% of 44 unrelated healthy females (36). A study of patients with rare bleeding disorders reported that HMB was presented in 44 out 50 women above the age of menarche (37). Another study from northern part India evaluating the type and frequency of hemostatic disorders among women with HMB, 35% were found to have hemostatic disorders including GT and BSS (38). A study among 108 women with HMB, found abnormal platelet function at the PFA-100 in 28,

17 patients showed platelet dysfunction, 7 with VWD and the rest undetermined (39). A retrospective study among 61 young patients with the history HMB showed platelet aggregation defects in 7% (40) and another 31% (41). Another study looked in 43 post-menopausal adolescents with menorrhagia and found a platelet function defect in 37 (86%) (42), while study in 74 women aged 17 -55 with unexplained HMB found decreased platelet ATP release in 58.1 %, 19 of the patients had also a prolonged bleeding time, 16 had abnormal platelet aggregation and 13 had both (43). In a study where whole blood platelet aggregometry was performed, nearly one-third of those adolescents had platelet function abnormality (44). A small study of 14 adolescents with menorrhagia undergoing detailed hemostatic investigations, 2 VWD and 6-platelet dysfunction were found (45). Racial differences have also been reported and the prevalence of platelet function defects are being significantly more in black compared to white women with HMB. Though the correlation between bleeding disorders due to platelet function disorders and endometriosis has not been fully clarified, women with HMB seem to be at higher risk of developing or being diagnosed with endometriosis due to increased retrograde menstrual blood flow or bleeding from ectopic endometrial tissue (46). Certainly, many cases of endometriosis in women with GT have been reported.

5.3. Association between platelet aggregation defects and pathogenesis of endometriosis

As many studies have shown that platelets play a major role in the development of endometriosis. This association was explored in the study conducted by Davies *et al* (48). The study used case participants that were identified through a local hospital database that provided diagnostic information regarding laparoscopic procedures. The participants of the study

included 81 women aged between 18-55 years with surgically confirmed diagnoses of endometriosis. Participants with pre-existing conditions such as IBD, VWD, PFD and haemophilia or other rare factor deficiencies were excluded from the study. 30 asymptomatic control were members of staff from the hospital, without a diagnosis of endometriosis; they were matched, as far as possible, in ethnicity, blood group, and smoking status. Participants meeting the inclusion criteria were asked to complete the Pain Impact Questionnaire (PIQ-6), a six-question health survey designed to subjectively measure severity and impact of pain on an individual's functional health and wellbeing. Pictorial blood assessment chart (PBAC) were completed to semi objectively quantify menstrual blood loss. Laparoscopy were performed to determine the stage of endometriosis, and the revised American Society for Reproductive Medicine (rASRM) classification system was used to define disease severity (48). The primary indication for undergoing laparoscopy in women with endometriosis was: 51/81 (63%) for dysmenorrhea/pelvic pain, 10/81 (12%) for subfertility, 8/51 (10%) for ovarian cysts, and 6/81 (7%) for abnormal menstrual bleeding. Seven women (8.6%) had undergone hysterectomy for treatment of endometriosis. rASRM laparoscopic staging was available for 65 case participants and were distributed as followed: 18 (28%) women with stage I, 15 (23%) women with stage II, 14 (22%) women with stage III, and 18 (28%) with stage IV endometriosis. There was a considerably higher number of platelet aggregation defects seen among the women with one agonist, in comparison to the control group (31% versus 4%, $p = 0.005$)(56). Furthermore, there were substantially higher abnormal aggregation responses to multiple agonists (≥ 2) in women with endometriosis (15% versus 4%, $p < 0.05$). Women with endometriosis had significantly increased mean PBAC score compared to controls (319, SD ±366 in case group vs 147, SD ±166 in controls, $p = 0.024$). No statistically significant difference was detected between any hemostatic variable and the PBAC score. However, the mean PBAC score was

significantly increased in women with platelet aggregation defects to one agonist (408, SD ±418, p = 0.021), and multiple agonists (489, SD ±589, p = 0.015) compared to the mean PBAC score of women without platelet aggregation defects (266, SD ±297). Platelet count was the only hemostatic variable to demonstrate a weak positive correlation with PIQ-6 score in the logistic regression analysis (r2 = 0.031, p = 0.03) (48).

An increased frequency of abnormal platelet aggregation and low VWF:RCo were prominent in women with endometriosis (48). This implies that primary hemostasis defects are associated with stage IV endometriosis. These outcomes correlate with the pathogenesis of endometriosis; an increased retrograde menstrual flow may result to a higher rate of development of endometriotic lesions. In addition, platelet activation induces overexpression of genes in ectopic endometrium that are involved in pro-survival/anti-apoptotic propensity, inflammation, angiogenesis, extracellular matrix (ECM) remodeling and the production of proinflammatory cytokines (29). Moreover, hemostasis defects with an endometriotic implant may result in repeated cyclic bleeding which in turn exacerbates the spread of the condition throughout the whole pelvic cavity. Ectopically implanted endometrial tissues are continuously under hormonal regulation and experiences monthly proliferation and shedding. The pain is a result of localized internal bleeding within or around the endometrial deposits. A decrease in VWF activity levels with increased disease severity (stage IV) suggests that endometriosis may be associated with a functional defect in primary hemostasis (38).

Chronic inflammatory processes and continuous bleeding are associated with stage IV endometriosis, which may result in a consumptive microvascular process that could describe the decline in VWF levels. In addition, mild and moderate stages of endometriosis are more likely to be associated with local impaired hemostasis. Alternatively, impaired systemic platelet aggregation may result in progression to more advanced disease. Forthcoming research should

consider the VWF multimeric analysis in women found to have low VWF:RCo levels, which would help to determine the nature of the functional impairment. A vast majority of studies have suggested that there might be a relation between VWD and endometriosis (49). In a study that assessed the reproductive experience of women with VWD, endometriosis was reported in 30% of cases compared to 13% of controls (49). However, the increased detection of endometriosis may be higher in women with VWD, who suffer from HMB, and therefore are more likely to consult with a gynecologist. Women with severe endometriosis have been seen to have an increased platelet count. This has been previously confirmed (50). Thrombocytosis is thought to be a marker of chronic inflammation, and inflammation is strongly implicated in the pathogenesis of endometriosis (47).

Traditional testing of platelet function such as bleeding time, light transmission aggregation (LTA), impedance aggregometry, and investigation of platelet activation by flow cytometry require a high degree of expertise to perform and interpret and are limited to specialized hemostasis laboratories (51).

In addition, LTA is limited by lack of reproducibility. Thus, future research should address this, and any abnormalities found at initial testing should be reproducible. Thromboelastometry platelet mapping (TEGPM), primarily used to detect platelet inhibition to antiplatelet medication, is a novel method of assessing platelet function that is far more convenient for large scale studies (52). Routine testing for a disorder of primary hemostasis in women with endometriosis would be laborious and time consuming using traditional laboratory methods. On the other hand, a diagnosis of a PFD would aid treatment decisions in such cases; women with a positive diagnosis should be advised to avoid non-steroidal anti-inflammatory medication, which further impairs platelet function and is commonly used to treat the pain of endometriosis. In addition, it would be an important diagnosis to establish before undergoing surgical treatment. Abnormalities in platelet aggregation

detected with LTA do not always signify a bleeding disorder. An individual with suboptimal response to epinephrine only, and no bleeding history should not be considered as having a functional platelet abnormality with current clinical testing (42). All abnormalities in platelet aggregation found on initial testing should be repeated with the addition of flow cytometry, nucleotide studies, and genetic testing if appropriate to establish or exclude a diagnosis of PFD. Further research is required to determine whether the finding of a high frequency of abnormal platelet aggregation in women with endometriosis is detected in a larger cohort, ideally with control subjects including women who attend for laparoscopic sterilization. The impact of hemostatic treatment during menstruation should be investigated in women with endometriosis who are found to have a disorder of hemostasis. The effect of administering hemostatic therapy, in addition to hormonal treatment, to women with a primary hemostatic disorder and endometriosis should be assessed in a clinical trial. Antifibrinolytic agents (i.e. oral tranexamic acid) or DDAVP (i.e. intranasal desmopressin) can be administered prior to or during menses to assess the effect on endometriosis symptom severity and/or rate of endometriosis stage progression.

6. CONCLUSION

In conclusion this review demonstrates that platelet play a major role in the formation of endometriosis. Despite recent gains and knowledge the actual mechanisms remain unknown in most patients with impairment of platelet function. Women with platelet defects are more likely to suffer from bleeding episodes, heavy menstrual bleeding, post-partum hemorrhage, ovarian bleeding cysts, endometriosis, or bleeding complications at gynecological surgery as the main complications. Endometriosis is associated with a higher frequency of platelet aggregation. Women with severe (stage IV) endometriosis have reduced VWF activity levels. These findings could be explained by increased retrograde menstruation resulting in higher rate of 'seeding' within the pelvic cavity. An underlying contributor to the pathogenesis of endometriosis may be a primary defect in hemostasis, which can lead to disease progression.

The present review demonstrates that there is a significant correlation between bleeding disorders, predominantly platelet aggregation defects and endometriosis. Furthermore, anti platelet interventions have shown to effectively reduce endometriotic lesions and improve hyperalgesia in endometriosis.

Selective screening of symptomatic women with a positive bleeding history could have important implications for the treatment of endometriosis. Women found to have a co-existing platelet aggregation abnormality should be managed accordingly and advised to avoid antiplatelet medication. Finally, future research should aim to increase the understanding of platelet disorders in order to acquire significant strategies for the prevention diagnosis, therapy of bleeding and endometriosis.

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Biography

Mohammad Omar Rahimy is a highly motivated individual, who is numerate, and a reliable medical student with strong academic record. Once he completed his primary and secondary education in the Netherlands, he began his undergraduate Biomedical degree in London then successfully completed his master's degree in Cardiovascular Research from Kings College. Through these achievements he embarked his journey into medicine after being accepted in the University of Zagreb, School of Medicine in September 2014. During this time at the School of Medicine he worked as a student demonstrator in Gastroenterology Department under the supervision of dr.sc. Kalauz. He has undertaken relevant work experience in health care sectors in different countries. Being able to speak four different languages fluently and having vital work experience with both medical practitioners and patients, he possesses all the qualities, aptitude, and enthusiasm to make a positive contribution in the medical field. After graduating he will be looking forward to hone and enhance his current skill set and apply it to his future career in medicine.