Morphological and Histological Prenatal Studies on Some Structures of the Developing Human Knee Joint: Part 4-Histological observations on the prenatal neuroreceptors in the anterior cruciate ligament (ligamentum cruciatum anterius) ACL, synovial membrane (stratum synoviale) SM, and medial meniscus MM of the Developing human knee joint.

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Abstract: The neuroreceptors of the synovial joints had been studied in many species. The nuroreceptors of anterior cruciate ligament (ACL), synovial membrane(SM) and the medial meniscus (MM) of the developing prenatal human knee joint are insuffidient. The present work studies by light microscope the histology of some neuoreceptors of the (ACL), (SM) and (MM) of the developing prenatal human knee joint. Thirty three human male and female fetuses aged 4 months (13-16wks-CRL 9-14cm) and full term (33-36 weeks) (CRL 31-34cm) were used. Specimens were collected from the miscarages with no abnormalities or macerations from Al Zahra Hospital, Department of gynecology and obstetrics – Al Azhar university- Cairo –Eygypt. Dissection was done to expose the intraarticular structures. Specimens from the anteriorcruciate ligaments or its primordial ,the medial meniscus and the synovial membrane of the knees, of 4 months fetuses :(33-36 weeks) CRL 31-34cm) and :(33-36 weeks) CRL 31-34cm) full term were collected freshly and fixed in 10% formal saline solution for 10 days, dehydrated, cleared in benzene, embedded in paraffin wax, cut serially at 7 microns thickness then stained using Gordon and Sweet ,silver impregnation method.Histological examination of serial TS sections of parts of (ACL) of full term showed the presence of (8) types of neuronal like end structures,and free neve endings FNE,They were :1-Large Pacinian like corpuscles having onion-or broom like appearance with C T capsule and lamellate cell arrangement around a central core, with single axon ,the capsule continued with the endoneurium of the afferent nerve.2- (Ruffini like -end receptors) with ramifications,expanded terminal axon and terminals button ends, 3- ovoid Meissner- like Corpuscle with torous ending ,giving spiral appearance. 4-Big single elongated structures resembled Golgi tendon –organ, having large cluster components in CT capsule , 5-spray like neuronal structures with rows of nerve bundels arranged before and after.6- spindle –like structures with one axon 7-large varicosities nerve endings ,8 strange structure resembled flower.besides to atypical nerve endings. Pacinian corpuscles were the biggest, most prominent neurorecepors in ACL. Free nerve endings FNE , in one row and nerves plexus were present .The neuroreceptors occupied large surface area of ACL and SM,but littele surface area in MM.Histological examination of serial sections parts of TS of (SM) of full term showed the presence of 4 types of encapsulated neuroreceptors like stuctures,besides free nerve endings FNE: 1- Meissner -like Corpuscles shared one branched axon with spiral or zigzag nerve ending were near blood vessels , 2-Pacinian corpuscles of SM were in groups (botryoidal) around blood vessels,and were smaller than the Pacinian corpuscles in ACL.3-Raffini corpuscles were many, smaller than those present in ACL with button endings, 4- ovoid single big structures resembled Golgi tendon organ with periaxial space , large components and neurnal terminals in the capsule, were noted besides free nerve endings FNE. In the encapsulated neuroreceptors the neurlemma of the nerve joined the capsule of the nerve and the naked nerve fiber ran a wavy tortuous course inside the capsule .The myelin of the afferent nerve ended where the nerve entered the capsule. Histological examination of serial sections of parts of TS of(MM)of full term, showed the presence 1-Meissners -like Corpuscle with stacked modified flattened(Schwann) cells arranged transversely across the long axis of the corpuscle giving a striated appearance. The corpuscle had an upper open apex. The connective tissue corpuscle was continuous with the endoneurium , 2- Raffini nerve like endings with ramified,expanded ends, and terminal buttons, were noted ,besides few free nerve endings that were in the fetus aged 4month ,and increased in full term. The presence of Meissner Corpuscle in the ACL, SM,MM in the prenatal developing human knee joint was not REPORTED in the literature.Previous workers identified and classified morphologically the -neuro reseptos in the synovial joints in many specieses and adult human knee joint into only four types. Raffini, Pacinian corpuscles, Golgi tendon organ besides free nerve endings FNE. Conclusion: In the present study , encapsulated neuroreceptors (mechanoreceptors) like structures and free nerve endings FNE in the in the(ACL), (SM) and(MM) in the prenatal

developing human knee joint were seen .Based on these findings,the presence of these neuroreceptors like structures in (ACL), (MM)and (SM)in the prenatal human knee joint indicated sensory function of these structures which subserved motion ,speed, acceleration, senses of movements, stress, position,vibration, temperature, pain, and discriminating afferent outflow to the central nervous system . That was to accommodate the functions of the knee joint intra-articular sructures as constrain of the prenatal human developing knee, biomechanics and kinematics. The complicated, numerous, various neuro like receptors and free nerve endings , in a minute , knee structures indicated the presence of the only powerful Creator , Allah .Suret Al Ensan 28, Suret Al thareate 21 .Suret Fusilate 53, Suret Lokman 11. Suret Fater 40, Allah sword on the truth of the Prophet of Islam by the stuctures that were not seen as these tiny neuroreceptors in thepresent work of the prenatal developing human knee joint,as they were seen only under microscope :suret el haka 39. Gordon and sweet -silver impregnation method illustrated neuroreceptors of the prenatal developing human knee. Meissner like Corpuscle In, ACL, S M, and MM, in the prenatal developing human knee were Not mentioned in the literature.More investigations are needed.
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Key words: Prenatal human Knee, anterior cruciate ligament, synovial membrane, medial meniscus, silver impregnation, neuroreceptors (mechanoreceptors).

Introduction:

Freeman and Wyke 1967 studied the knee joints of cats and classified encapsulated nerve endings in the synovium as follows: (Type 1); Ruffini endings were, slow adapting, low threshold mechanoreceptors, (Type 2); Pacinian corpuscles were, rapidly adapting ,low threshold mechanoreceptors, (Type 3); Golgi organs, with poor association with blood vessels were slowly adapting, high threshold, mechanoreceptors and (Type 4) free nerve endings were pain receptors.; Grönblad et al., pointed that the presence of nociceptive receptors in those joint structures, had been made on a histological basis, and were confirmed by immunohistochemical methods. Substance P-immunofluorescent nerves were associated with pain transmission and were found in human knee synovial membrane and menisci. Both tissues contained enkephalin-immunofluorescent nerves, which might be participated in pain modulation transmission.

El Rakawy (1971) classified nerve endings according their site into, to sensory nerve endings,called receptors and motor nerve endings called effectors, and according to whether they lied in the epithelium or connective tissue CT or muscle , according to whether they had a CT capsule called (encapsulated) or did not have a capsule called (non-capsulated), and according to their function as exteroceptors for pain, temperature (heat and cold)and touch; Proprioceptors that conveyed sensation from muscles, tendons and in C.T. near the joints.besides to visceroceptors that conveyed sensation from viscera.

Arnoczky (1983) and Mommersteage et al. (1995) mentioned that the nerve supply to anterior cruciate ligament (ACL) originated from the tibial nerve .Although the majority of the fibers had vasomotor function, some fibers might serve proprioceptive or sensory function. The anterior cruciate ligament (ACL) in adult was multi fascicular structure with femoral and tibial attachment, and its spatial orientation in the knee was directly related to its function as a constrain of joint motion.

Zimny et al. (1986) mapped the anterior cruciate ligament ACL, using a computerized, morphometric analysis and, obtained the percentage of receptors in in each ACL .Their study was undertaken to quantitate and identify mechanoreceptors in the human anterior cruciate ligament (ACL). They obtained Ligaments from six human subjects were at autopsy, cut into cross-sectional segments 1.0-1.5 cm thick, and kept oriented as to the femoral and tibial attachments. They stained segments in bulk by using a modified gold chloride method, then frozen, and sectioned on a sliding microtome at 100 microns. The sections were floated in alcoholic gelatin, mounted on slides, dehydrated, and cover slipped. They studied with the light microscope serial sections of the receptors and photographed them. They made cross-sectional maps of every tenth section outlining the periphery of the ACL and the receptors within that section. They found that free nerve endings, and two morphologically mechanoreceptors were identified: (1) Ruffini end organs and (2) Pacinian corpuscles. Their preliminary morphometric analysis showed that the mechanoreceptors were greater at the femoral and tibial ends of the ligament and constituted approximately 2.5% of the ligament. Based on those findings, they convluded that the human ACL had the anatomic basis for a discriminating afferent outflow to the central nervous system.

Schutte et al. (1987) identified in the anterior cruciate ligament, in human cadavers, besides the free nerve endings, Raffini slowly adapting type and, rapidly adapting Pacinian corpuscle. The rapidly adapting receptors signaled motion and slowly adapting receptors subsurved speed and acceleration. Free nerve endings, were responsible for pain. Those neural elements comprised one per cent of the area of anterior cruciate ligament.

Halata and Haus (1989) studied the sensory innervation of the anterior cruciate ligament (ligamentum cruciatum anterius) of the human knee joint by light- and electron microscopy. They found that the connective tissue between the synovial membrane and the cruciate ligament contained small Ruffini corpuscles and lamellar corpuscles with several inner cores. The connective tissue septa between the individual fascicles of the cruciate ligament contained Ruffini corpuscles and free nerve endings. The free nerve endings were innervated by C-fibres and myelinated A-delta fibres. The afferent axons of Ruffini corpuscles were myelinated and measure 4-6 microns in diameter; those of the lamellar corpuscles with several inner cores measure about 6 microns in diameter. They discussed, whether these receptors of the anterior cruciate ligament mjght influence the muscle tone via polysynaptic reflexes

Johansson et al. (1991) reviewed the morphologic, physiologic, and clinical evidence for the sensory role of the cruciate ligaments. They concluded that, the sensory system of the cruciate ligaments was significantly contributed to the functional stability of the knee joint by preprogramming of the muscular stiffness around the knee joint and thereby of the knee joint stiffness.They found that the cruciate ligaments accommodated morphologically different sensory nerve endings with different capabilities of providing the central nervous system with information about noxious , chemical situation and stretches ,besides characteristics of movements and position of those ligaments: They found (Ruffini endings, Pacinian corpuscles, Golgi tendon organ like endings, and free nerve endings). Their survey of the available data revealed that low threshold joint-ligament receptor (i.e., mechanoreceptor) afferents evoked only weak and rare effects in skeletomotor neurons (alpha-motor neurons), while they frequently and powerfully influenced fusimotor neurons (gamma-motor neurons). They added that the effects on the gamma-muscle-spindle system in the muscles around the knee were so potent that even stretches of the cruciate ligaments at relatively moderate loads (not noxious) might induce major changes in responses of the muscle spindle afferents. As the activity in the primary muscle spindle afferents modified the stiffness in the muscles, the cruciate ligament receptors, via the gamma-muscle-spindle system, might participate in the regulation and preprogramming of the muscular stiffness around the knee joint and thereby of the knee joint stiffness.

Katonis eral.,(1991) found in addition to free nerve endings, in the healthy human posterior cruciate ligament, two types of mechanoreceptors .They were located at the femoral and tibial attachments, and on the surface of the ligament .

Zimny , Wink (1991) mentioned that Ruffini mechanoreceptors contributed mainly to maintenance of muscle tone, Pacinian corpuscles and Golgi tendon organs were stimulated during movement, and free nerve endings were nociceptors. Thus, receptors of the knee joint were able to produce a discriminating afferent inflow to the central nervous system (CNS), thereby contributing to the protection and function of the joint through the musculature. They stated that four types of receptors had been described in the articular tissues of the knee joint in humans and animals. The first three types were encapsulated; the fourth was unencapsulated: type I, Ruffini endings; type II, Pacinian corpuscles; type III, Golgi tendon organs; and type IV, free nerve endings. Ruffini endings, Pacinian corpuscles, and free nerve endings were most prevalent in the fibrous joint capsule; Golgi tendon organs were most common in the collateral and cruciate ligaments and the menisci. In the anterior and posterior cruciate ligaments (ACL, PCL), receptors were concentrated at the tibial and femoral attachments of the ligaments. In the menisci, neural elements penetrated the horns and the outer and middle thirds of the body.

Biedert et al. (1992) studied the qualitative and quantitative measurements of the incidence of free nerve endings of the knee joint .They found the highest amount of afferent nerve fibers type IV were found in the retinacula, the patellar ligament, and the pes anserinus. Their study was made on the histology in18 static and dynamic structures of 8 cadaveric knees. They noted positive correlation between the number of mechanoreceptors per standardized area unit and the clinical presentation of certain knee disorders.

Gartner and Hiatt (1994) described Meissner's corpuscle in Paraffin sections stained by H&E stain as oval encapsulated mechanoreceptors lying in dermal ridges just deep to the stratum germinativum. They were especially prominent in the genital area,lips,fingers,and sole of feet .A connective tissue capsule enveloped the corpuscle .The nuclei within the corpuscle belonged to flattened probably modified Schwan cells ,which were arranged horizontally in that structure. The afferent nerve fiber pierced the base of Meissner's corpuscle, branched, and followed a tortuous course within the corpuscle.

Gartner and Hiatt (1994) explained that Pacinian corpuscle mechanoreceptors were,located in the dermis and hypodermis .They were composed of a core with an inner and outer regions, and a capsule which surrounded the core. The inner core invested the afferent nerve fiber which lost its myelin sheath soon after entering the corpuscle. The core cells were modified Schwan cells, while the component of the corpuscle was continuous, with the endoneurium of the afferent nerve fiber. Pacinian corpuscle resembled the cut onion.

Krauspe et al. (1995) studied the distribution of neuro filament positive nerve fibers and sensory endings in the human anterior cruciate ligament .They described two types of corpuscular -like endings were found i.e. "spiral like "type I and spray like"type II endings .Similarly to nerve fibers, both types of corpuscular -like endings were found mainly near the tibial and femoral attachment sites. They added that most likely "type I and "type II corpuscular -like endings served a mechanoreceptive function involved in the sensory control of normal movements and stress function.

Amir et al. (1995) analyzed the innervation in adult cruciate ligament in osteoarthritis and in idiopathic gonarthrosis. They found statistically significantly greater area of nerve tissue around the anterior cruciate ligament in osteoarthritis group than around the ligaments in the control group. They proved morphological evidence for neural pathology of the anterior cruciate ligament in subjects with osteoarthritis.

Grönblad et al. (1985) confirmed by a specific immunohistochemical method,the presence of nociceptive receptors in human knee synovial membrane and menisci and confirmed the histology of those non-cartilaginous joint structures,.They showed Substance P-immunofluorescent nerves, which were closely connected to pain transmission, Both tissues also contained enkephalin-immunofluorescent nerves, which were probably involved in the modulation of pain transmission.

Schenk et al. (1996) studied the ultrastructure and distribution patterns of sensory nerve endings in the dorsal knee joint capsules of the beagle dog (Canis familiaris) using light and electron microscopy. They found different sized Ruffini corpuscles: very small, small, medium. large. Ruffini corpuscles were present as single, cylindrical structures (small corpuscles) or as aggregates of these cylinders (large corpuscles). Both varieties consisted of terminal nerve endings surrounded by collagen fibres which passed through the opened ends of the cylinders. No nerve endings within the synovial layer. Free nerve endings were usually situated at the border between the fibrous layer and the synovial layer near blood vessels.

Gray (1999) reviewed the general anatomy, vascular anatomy, healing potential, neural anatomy, and sensory functions of the menisci of the human knee. They mentioned important roles and functions of the menisci of the human knee. They made a medline search using the following title and key words: menisci, meniscus, meniscal, vascular, blood, neural, nerve, anatomy, healing, sensory, mechanorecepton, proprioception, nocicepton, surgery, meniscectomy, repair, and rehabilitation. The references from each article obtained were then reviewed in order to find additional articles not already located through the Medline search. They dound in adults, the blood supply to the menisci of the knee reached the outer 10% to 33% of the body of the menisci. That portion of the menisci was capable of inflammation, repair, and remodeling. Neural innervation with nociceptors and type I, II, and Ill mechanorecepton reached the outer 66% of the body of the menisci. The anterior and posterior horns of the menisci had a rich supply of both blood vessels and nerves. They concluded that menisci of the human knee were an important source of proprioceptive information regarding the position, direction, velocity, and acceleration and deceleration of the knee. Rehabilitation following injury or surgery to the menisci of the knee should, therefore, incorporate a proprioceptive retraining program that respected both the abilities and inabilities of different portions of the menisci to follow through with repair and remodeling. Sparmann et al. (1996) found significant loss of innervation of anterior cruciate ligament in idiopathic gonarthrosis. They wandered if that was the reason for the arthritis or was a secondary phenomenon.

Maeda et al. (1999) noted that the periodontal ligament received a rich sensory nerve supply and contained many nociceptors and mechanoreceptors. They pointed that, only recently had studies revealed that the Ruffini endings--categorized as low-threshold, slowly adapting, type II mechanoreceptors--were the primary mechanoreceptors in the periodontal ligament.

Snell (2010) mentioned that in Joint receptors, four types of sensory receptors could be located in the capsule and ligaments of synovial joints. Three of those endings were encapsulated and resembled pacinian, Ruffini, and tendon stretch receptors. They provided the central nervous system with information regarding the position and movement of the joint .A fourth type of ending was non encapsulated and was thought to be sensitive to excessive movement and transmit pain sensations.

Krebs et al. (2012) classified mechanorecepto according to their location and receptor field into either slowly or rapidly adapting. Type 1 mechanoreceptor were Meissener and Merekel disks lied superficially at the boundary of epidermis and dermis and had small well defined receptor field. Type 11 mechanoreceptor e.g Pacinian corpuscles were positioned deep in the dermis and had large, poorly defined receptor fields. Pacinian corpuscles detected vibration and Ruffini detected stretch .They added that Raffini endings receptors had a thin capsule and a mesh of longitudinal arranged collagen fibers without the capsule, Sensory fibers branched throughout the strands collagen fibers. They were slowly adapting and detected skin stretch and pressure.

Turlough Fitzgerald et al. (2012) mentioned that the capsules of the three nerve endings had to be described comprised an outer coat of modified Schwann cells(telogalia).All three were mechanoreceptor transducing mechanical stimuli.Meissner s corpuscles were most numerous in the finger pads. Where they lied beside the intermediate ridges of the epidermis. بلي قادرين علي أن نسوي بنانه سورة القيامة4In these ovoid receptors, several axons zigzaz among stacks of teloglial lamellae. Meissner s corpuscles were rapidly adapting .Together with the slowly adapting Merkel cell neurite complexes; they provided the tools for delicate detective work on textured surfaces such as cloth or wood, or on embossed surfaces such as Braille text. Elevations as little as 5um in height could be detected.

Standring et al. (2016) reported that the different types of sensory endings showed activation at different developmental times. Mechanoreceptors and proprioceptors were active ahead of nociceptive neurons prenatally. A third wave of mechanosensetivity acquisition by the remaining nociceptors occurred just after birth.

Splittgerber (2019) reported that the different types of receptors were previously thought to correspond to specific types of sensation,until recently scientists pointed out that some areas in the body had only one or two histological types of receptors and were sensitive to a variety of different stimuli.Moreover,although the body had those different receptors,all nerves only transmitted nerve impulses.Now scientists generally agreed that the types of sensation felt was determined by the specific area in the CNS to which the afferent nerve fiber , passed.For example,if a pain nerve fiber was stimulated by heat,cold, touch,or pressure,the individual would experience only pain

Belluzz et al. (2019 reported that, sensory nerve fibers were involved in pain perception and in the secretion of proinflammatory SP, while sympathetic nerve fibers secreted anti-inflammatory catecholamine (in particular norepinephrine and endogenous opioids) inhibiting pain perception, it was likely that a cross-talk with sensory fibers might exsist.They illustrated that, the synovium in the synovial Joints, had dense innervation by sympathetic nerve fibers. Tyrosine hydroxylase (TH) was the common marker used to identify catecholaminergic nerve fibers Mach et al 2002. TH positive sympathetic nerve fibers were found in infra patellar pad of fat IFP of osteo arthritis OA patients . Synovial membrane of OA patients had a higher number of sympathetic nerve fibers (TH positive) but less number of TH positive cells (fibroblasts, macrophages, B cells, mast cells, and granulocytes) producing catecholamines than RA patients

Snell (2010) and Splittgerber (2019) reported that free nerve endings were widely distributed throughout the body .They were found between the epithelial cells of the skin, the cornea, the alimentary tract and in connective tissues ,including the dermis ,fascia, ligaments, joint capsules, tendons ,periosteum, perichondrium, havertian system of bone ,tympanic membrane and dental pulp. They were also present in the muscle. The afferent nerve fiber formed the free nerve endings were either mylinated or non mylinated. The terminal endings were devoid of myelin sheath, and there were no Schwan cells covering their tips. Most of those detected pain, while others detected crude touch, pressure, tickle sensation and possibly cold and heat.

• Çabuk and Çabuk 2016 mentioned that proprioceptive inputs from the joints and limbs arised from mechanoreceptors in the muscles, ligaments and tendons. The knee joint had a wide range of movements, and proper neuroanatomical organization was critical for knee stability. Çabuk and Çabuk2016 harvested four ligaments (the anterior (ACL) and posterior (PCL) cruciate ligaments and the medial (MCL) and lateral (LCL) collateral ligaments) and four tendons (the semitendinosus (STT), gracilis (GT), popliteal (PoT), and patellar (PaT) tendons) from eight fresh frozen cadavers Each harvested tissue was divided into its bone insertion side and its tendinous part for immunohistochemical examination using S100 staining. Çabuk and Çabuk used Freeman -Wyke's classification to identify the mechanoreceptors. They foud that mechanoreceptors were usually located close to the bone insertion. Free nerve endings followed by Ruffini endings were the most common mechanoreceptors overall. No Pacini corpuscles were observed; free nerve endings and Golgi-like endings were most frequent in the PCL (PCL-PaT: $P = 0.0.1$, PCL-STT: $P = 0.00$), and Ruffini endings in the popliteal tendon (PoT-PaT: $P = 0.00$, Pot-STT: $P = 0.00$, PoT-LCL: $P = 0.00$, PoT-GT: $P = 0.00$, PoT-ACL: $P = 0.09$). The cruciate ligaments had more mechanoreceptors than the medial structures (MS) or the patellar tendon (CR-Pat: $P = 0.000$, CR-MS: $P = 0.01$). They cocluded that differences in mechanoreceptor distributions between the ligaments and tendons could reflect the different roles of those structures in the dynamic coordination of knee motion.

Sadler (2019) mentioned that, unlike Schwann cells,a single oligodenroglial cell could mylelinate up to 50 axons. Although mylelination of nerve fibers the spinal cord ,began in approximately the fourth month in the intrauterine life,some of the motor fibers descending from higher brain centers to the spinal cord,did not become mylelinated until the first year of postnatal life .Tracts in the nervous system became mylinated at about the time they started to function . Schwann cells mylelinated the peripheral nerves with each cell myelinating only as single axon. Those cells originated from the neural crest, migrated peripherally and wrapped themselves around axons forming the neurilemma sheath. Beginning at the fourth month of fetal life, many nerve fibers took on a whitish appearance as a result of deposition of myelin, which was formed by repeated coiling of the Schwann cell membrane around the axon. The myelin sheath surrounding nerve fibers in the spinal cord had a completely different origin.

Meghan et al. (2022) reported that Professor Georg Meissner and Professor Rudolf Wagner in 1852 first described Meissner corpuscles, also known as Wagner-Meissner corpuscles or tactile corpuscles. They were specialized encapsulated nerve endings relayed fine touch and low-frequency vibration sensations to the central nervous system (CNS). They were a subset of mechanoreceptors. Located in the dermal papillae of glabrous skin,. Meissner corpuscles played an essential role in somatosensory acuity, especially in the digital extremities and palmar skin, meriting clinical significance for peripheral and diabetic neuropathy as well as age-related degeneration of dermatological tactile sensation. Meissner corpuscles consistedof a cutaneous nerve ending responsible for transmitting the sensations of fine, discriminative touch and vibration (Vega et al., 2012) and relay of pain sensations, as some axons might express substance P and other nociceptive peptides. Paré et al. (2001)Meissner corpuscles were most sensitive to low-frequency vibrations between 10 to 50 Hertz and could respond to skin indentations of less than 10 micrometers. Additionally, these corpuscles might detect the sensation of slip between an object and the skin, allowing for grip control.

Meghan et al. (2022) mentioned that the development of Meissner corpuscles was dependent on brain-derived neurotrophic receptor (BDNF) signaling via tropomyosin receptor kinase B (TrkB). TrkB was an enzyme-linked transmembrane receptor encoded by the NTRK2 gene. Animal studies involving knockout of BDNF or TrkB in mice resulted in a lack of Meissner corpuscles, indicating the importance of that signaling system in corpuscular development (González-Martínez et al., 2004&2005; Ichikawa et al., 2000)

Banios et al. (2022) reviewed the mechanoreceptors in the anterior and posterior cruciate ligaments and grafts mechanoreceptors, and their role in proprioception of knee joint, focusing on each type of mechanoreceptors .They reported that proprioception was a specialized sensory modality involving the joint movement and its position in space, besides conversion of mechanical deformation of tissues into neural signals. Mechanoreceptors MRCs were specialized nerve structures abled to transmit mechanical deformation through electrical signals to neurons of dorsal root sensory ganglia and were abundant in the muscles, ligaments and tendons of the knee joint. They were believed to have an important role in knee stability, proprioception and dynamic. Proprioception should be considered for successful reconstruction of the cruciate-deficient knee and management for function and pain in the arthritic knee. Advances in histological methods for mechanoreceptors detection and their role were numerous and continued to highlight their influence and presence after ligament reconstruction, depending on graft choice.

Banios et al. (2022) concluded that further research was required to understand the full role of mechanoreceptors. Understanding the role of MRCs in knee kinematics would provide more information about the proprioceptive deficiencies accompanied ligament ruptures and the pathogeneses of knee arthrosis. Patients at risk for MRCs-deficient knees had to be managed with special rehabilitation protocols to compensate for proprioception loss and kinesthesia.

Banios et al. (2022) mentioned that the knee joint was a complicated structures of osseous and soft tissue components that worked together to allow three planes of motion. The ligaments were the static stabilizers of the knee. The cruciate ligaments were the main restraints of tibial translation relative to femur. In particular, the posterior cruciate ligament (PCL) prevented the posterior translation of tibia and, acting as a counterpart to the ACL anterior cruciate which prevented the anterior translation of tibia (Frank, 2004)

Both the anterior ACL and posterior PCL cruciate ligaments had contributed to dynamic stability of the knee joint via proprioception and activation of knee muscles ,besides being the main restraint against anterior or posterior translation of the tibia relative to the femur. Interest in the presence and function of mechanoreceptors (MRCs) that were responsible for proprioceptive function in the ACL and PCL had occurred recently. Many studies demonstrated that MRCs were present in both ligaments (Frank et al., 2004; Godinho et al., 2014; Freeman and Wyke, 1967, Zimny et al., 1986, Denti et al.,1994 .

Banios et al. (2022) mentioned that proprioception was a specialized sensory modality encompassing the movement of the joint and its position in space. There were three main functions of proprioception:

1. Static awareness of joint position;
2. Awareness of joint movement and acceleration;
3. Reflex responding and regulating muscle activity.

Proprioception had an important role in preventing injuries and maintaining function of the knee joint (Freeman and Wyke 967). The sense of proprioception involved MRCs, which were specialized nerve structures abled to transmit mechanical deformation through electrical signals to dorsal root ganglion sensory neurons. Mechanoreceptor was a subtype of somatosensory receptor. It conveyed extracellular stimuli through intracellular signal conduction via a mechanically gated ion channel. It conveyed not only kinetic stimuli, but also pressure, stretching, touch, and even sound wave.

يوم تشهد عليهم ألسنتهم وأيديهم وأرجلهم بما كانوا يعملون سورة النور24

وتكلمنا أيديهم و تشهد أرجلهم بما كانوا يكسبون .سورة يس 65

أنطقنا الله الذي أنطق كل شيء. سورة فصلت21

سنريهم اياتنا في الآفاق وفي أنفسهم حتي ينبين لهم أنه الحق. سورة فصلت53

There were four types of MRCs classified by Freeman and Wyke present in knee joints of the cat:

Type I: corpuscles of Ruffini low-threshold, slowly adapting receptors that responded to mechanical stress. Ruffini endings appeared to be stimulated by displacement of the collagen fibers with which they were intertwined. Ruffini receptors endings were static and dynamic mechanoreceptors, transmitting information about static position, changes in intra-articular, pressure, amplitude, direction and velocity of the joint movements.

Type II: corpuscles of Vater-Pacini—dynamic, rapidly adapting mechanoreceptors having low threshold. They were inactive in immobile joints, becoming active only at the onset or cessation of joint movement, moments at which sudden changes of stress occurred.

Type III: Golgi corpuscles—high threshold, slowly adapting mechanoreceptors that were completely inactive in immobile joints. They became active only in extreme ranges of movement and when considerable stress was generated in the joint.

Type IV: free nerve endings—high-threshold, non-adapting pain receptors.

Various histological methods had been used in identifying MRCs mostly using the gold chloride method [Zimny et al., 1986, Denti et al., 1994.

Recently, immunological methods using specific antigen antibody reactions had been increasingly utilized (Meghan et al., 2022). Immunological methods were more reliable and easier to use compared to the traditional methods of histological staining. Histological staining methods most commonly identified the structurally normal MRCs only, while the immunological stains identified the functionally viable MRCs [ ]. Three antibodies were widely used in immunohistochemical analysis of neuronal structures and had proven to be the most reliable method in the detection of MRCs: the polyclonal antibody against S-100, the one against p75 and the monoclonal antibody against PGP9.5 (Rebmann, 2020).

Aim of the work

Many studies on nerve receptors in the synovial joints in human and different species were published. However, there is insufficient studies on the neuroreceptors of the prenatal developing human knee joint. The aim of the present work is to find out some observations on the neuroreceptors in the anterior cruciate ligament, synovial membrane and the medial meniscus, of the developing prenatal human knee joint. The understanding of the anatomical function of theseneuronal structures of the developing prenatal human knee joint might help preserve knee biomechanicks and improve treatment of knee lesions.

Material and methods:

33 Human (male and female) fresh fetuses aged 4 fetuses :(33-36 weeks) CRL 31-34cm) and 9 months full term:(33-36 weeks) CRL 31-34cm) were used in this investigation. The fetuses were obtained from the miscarriage and spontaneous abortion obtained from Gynecology and Obstetrics Department Al -Zharaa hospital-Cairo -Egypt (according to medical ethics) .They were used to study nuroreceptors in anterior cruciate ligament, medial meniscus and synovial membrane in the prenatal developing human knee joint. Dissection of both sides of the developing knees held according to Romanes (2000) in three stages: a) to expose the outermost structures of the joint's cavity, by cutting across the quadriceps tendon immediately proximal to patella. Then the latter was turned downwards. followed by displacement of the capsule ;b) A deeper dissection was done to expose the intraarticular structures, by removing the infrapatellar (IPF) synovial fold and fat, then the infrapatellar bursa was opened. c) A clear view of the upper surface of the tibia was obtained after cutting across the fibular and tibial collateral ligaments, the arcuate ligament, tendon of popliteus and the remains of the fibrous capsule. Followed by cutting across the cruciate ligaments. Then specimens were fixed in formalin For histological study, specimens from the anterior cruciate ligaments and the medial menisci of the knees, as well as the synovial membrane of 4 months fetuses :(33-36 weeks) CRL 31-34cm) and full term:(33-36 weeks) CRL 31-34cm) were collected freshly and fixed in 10% formal saline solution for 10 days, then dehydrated, cleared in benzene, embedded in paraffin wax, cut serially at 7 microns thickness and then stained

by Gordon and Sweet –silver impregnation to illustrate the neuroreceptors and free nerve endings in the anterior cruciate ligament , medial meniscus and synovial membrane. The impregnating solution composed of urea, 1% silver nitrate, 95% ethyl alcohol, pyridine, 1% mercuric cyanide, and 1% picric acid in distilled water. After incubation for 5.5 hours, the specimens were submerged in a solution of 1% hydroquinone, 5% anhydrous sodium sulfate, and urea, followed by a mixture of 0.2% gold chloride and glacial acetic acid, then 5% sodium hyposulfite.Drury and Wallington (1980).

Results:

Morhological Results: Figs.A, B&C

Morhological examination of of 4 month fetus (13-16wks-CRL 9-14cm) showed the condyles of the lower end of the femur were articulating with the medial and lateral meniscus on the upper surface of the tibia of the knee joint, and the intercondyler area had tan intra articular septum ;the septum genuwhich represented tge cruciate premrdium. Fig. A

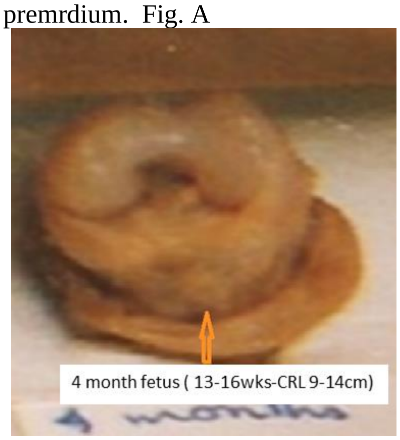


Fig.(A): A photograph of the knee joint anterior view full flexion positionof 4 month fetus (13-16wks-CRL 9-14cm) showing the condyles of the lower end of the femur is articulating with the medial and lateral Meniscus on the upper surface of the tibia of the knee joint and the intercondyler area had tan intra articular septum ;the septum genuwhich represented tge cruciate premrdium

Morhological examination of of of left knee of full term infant (40 weeks old) showing that the medial and the lateral femoral condyles of the lower end of the femur.were articulating with the medial and lateral menisci on the upper surface of the tibia of the knee joint. The cruciate ligaments attachmented to the intercondyler area

The synovial membrane surrounded the knee joint. Fig. B

Morhological examination of the right knee joint of full term Showed the intra articular septum was between media and lateral condyle and was differentiated into three bands, posterior, and anterior cruciate ligaments and meniscofemoral ligament . Fig. C)

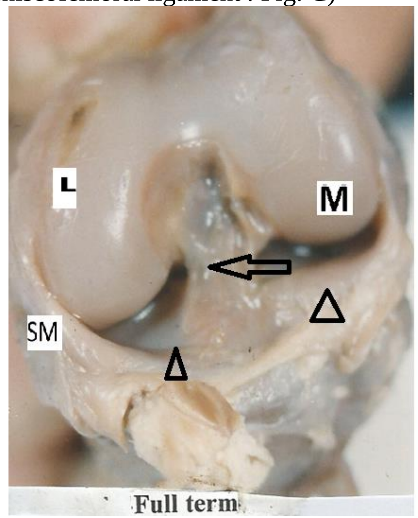


Fig. (B): photograph of left knee of full term infant (40 weeks old) showing that the medial (M)and the lateral femoral condyles(L) of the lower end of the femur.(F) are articulating with the medial and lateral meniscus M (head arrow)on the upper surface of the tibia of the knee joint .

Notice the attachment of the cruciate ligaments CL (arrow)in the intercondyler area

The synovial membrane SM.

Medial and the lateral femoral condyles of the femur were articulating with the medial and lateral meniscus on the upper surface of the tibia of the knee joint.

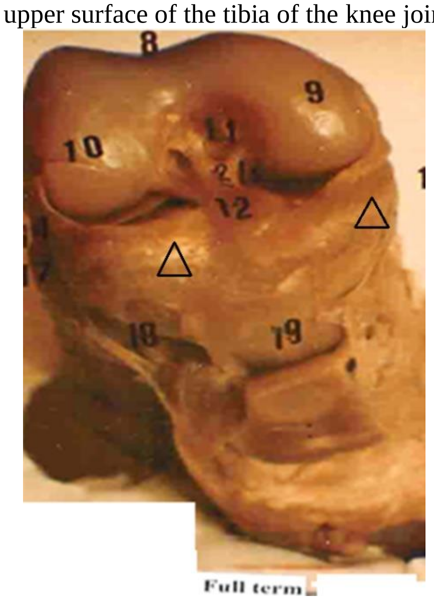


Fig. (C): A photograph of the right knee joint of full term Showing the, intra articular septum is between medial (9) and lateral condyle (10) and is differentiated into three bands, posterior (11) and anterior (12) cruciate ligaments and meniscofemoral ligament (21).

Medial and the lateral femoral condyles of the femur. (Are articulating with the medial and lateral meniscus (head arrow) on the upper surface of the tibia of the knee joint .

Histological Results:

Anterior cruciate ligament:ACL (Figs.1-5) and (tables 1-5) Histological examination of parts of TS serial sections stained by silver impregnation - Gordon and Sweet method of parts of anterior cruciate ligament ACL of full term human:(33-36 weeks) CRL 31-34cm): showed the presence of spindle like structures with one axon (Figs. 1&4) and the numerous spiral and zigzag encapsulated nerve ending in Meissener like corpuscle . Single elongated Golgi like organ, with many large component ib thevcapsule (Figs (1&4). Free nerve endings Figs(1,2&3): Bundles of nerve fibers arranged in one row before and after the spray struvture, and plexus of nerves were noted Figs(3&4). Structure similar to flower (fl) was seen (Fig2).

large Pacinian corpuscles (Figs 3,4&5) were present formed of layers of cells arranged in lamellae darkly stained around a core , and the capsule of Pacinian corpuscle was continuous with the endoneurium of the afferent nerve.Some Pacinian corpuscles simulated cut onion structure ,other corpusles were broom life.

Spray like structures were noted (Figs. 3&4). Raffini nerve end like –corpuscles were seen and had a branched axon terminals Fig. (4).Axons, were surrounded by thin Schwann cell processes, were embedded in the dense layers of collagen fibrils. The interior of the corpuscle was separated into small compartments by cell processes extended from the capsule.displayed dendritic ramifications with expanded terminal axon and terminal buttons ends (Figs .4&5). Lamellar Schwann cells associated the Raffini corpuscle like endings. Finger-like projections called axonal spines or microspikes, extend into the surrounding tissue were seen (Figs. 4 & 5).

Large neural elements like varicosities under the incomplete capsule were seen Fig. (4)

Large oval single Golgi tendon like –organ with large components and sensory terminals in a capsule (Figs4&.5) was seen

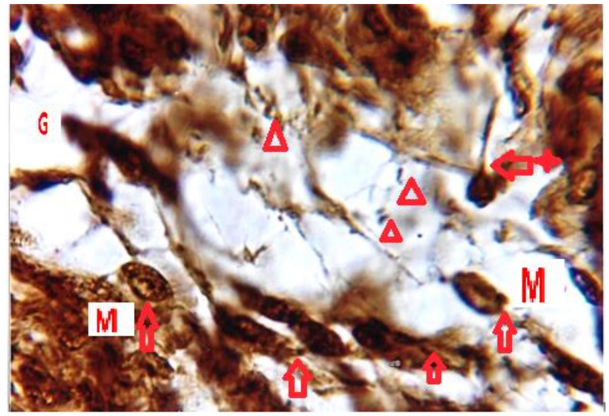
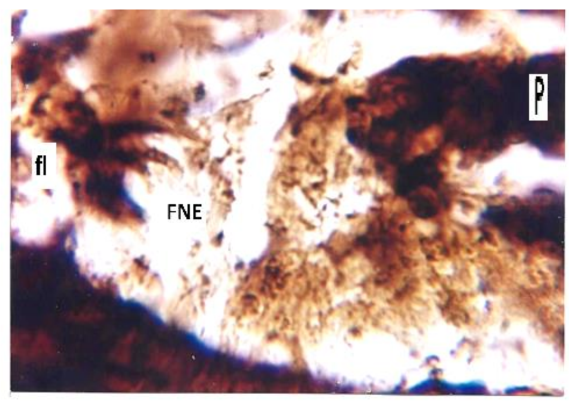


Fig. (1): Photomicrograph of part of TS of part of anterior cruciate ligament of full term human :(33-36 weeks) CRL 31-34cm): showing fusiform structure (arow-star).
Note the numerous spiral and zigzag encapsulated nerve ending in Meissener like corpuscle (Marrow)
Free nerve endings (arrowhead)
Note the Golgi like organ (G)
Gordon and Sweet Silver impregnation x1000



Fig(2): Photomicrograph of part of TS of part of anterior cruciate ligament of full term human:(33-36 weeks) showing Free)nerve endings (FNE) and Strange structure similar to flower (fl)
Note the appearance of part of Pacinian corpuscle (P)
Gordon and Sweet Silver impregnation x1000

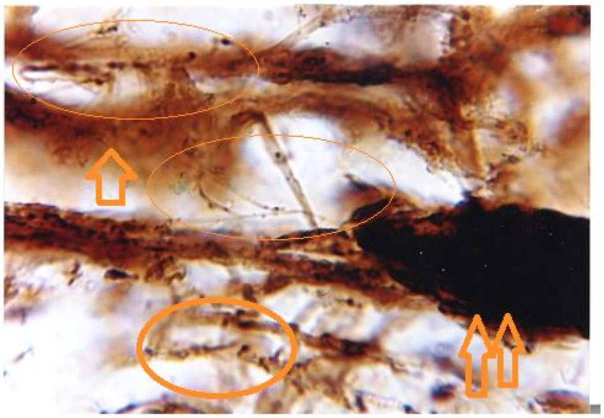


Fig (3): Photomicrograph of part of TS of part of anterior cruciate ligament ACL of full term human :(33-36 weeks) CRL 31-34cm): showing spray like structure (arrow)
Notice the nerves are arranged in one row before and behind the spray structure.
Note: the bundles of nerves and plexus (circle).
Notice the Pacini corpusle is large and broon like (double arrow) with flat lamellate cells.
Notice: that the endoneiurium is continuous with the capsule of Pacini corpusle.
Gordon and Sweet Silver impregnation x1000

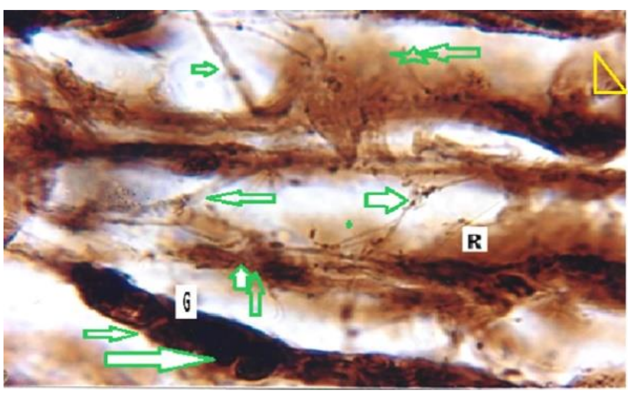


Fig (4): Photomicrograph of part of TS of part of the anterior cruciate ligament ACLof full term human: (33-36 weeks) CRL 31-34cm): showing spray like structure (star-arrow)
Notice: the row of nerves bundles communicating as plexus (empty arrow) and with Raffini ends (white solid arrow).
Notice: the small spindle like structure (double arrows: white &empty)
Notice: that the Ruffini endings display dendritic ramifications with expanded terminal axon and terminal buttons ends (R)
Notice the finger-like projections called axonal spines or microspikes, which extend into the surrounding tissue.

Notice the terminal or lamellar Schwann cells associate the Raffini corpuscle like ending,
Notice the Ruffini-type corpuscles, had branched axon terminals with varicosities under the incomplete capsule. Axons, were surrounded by thin Schwann cell processes, were embedded in the dense layers of collagen fibrils. The interior of the corpuscle was separated into small compartments by cell processes extended from the capsule.
Note the large oval elongated darkly stained structures similar to Golgi organ
(G)(Big thin long white arrow)
Gordon and Sweet Silver impregnation x1000

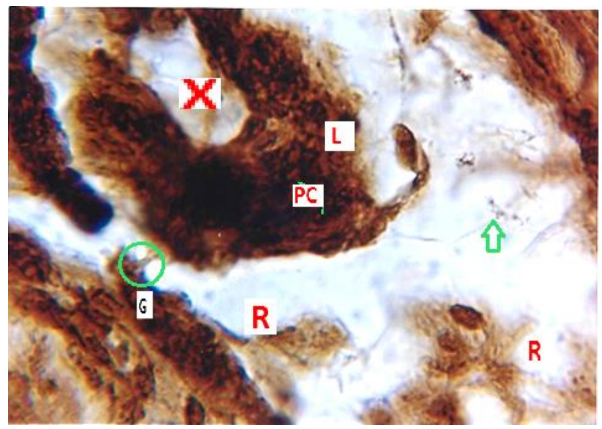


Fig. (5): Photomicrograph of part of TS of part of the anterior cruciate ligament of full term human :(33-36 weeks) CRL 31-34cm): showing large onion like structure Pacinian corpuscle (PC star), the connective tissue capsule is continuous with the endoneurum.
Note the lamellae forming the Pacinian corpuscle and the core is formed of naked axon.
Note the two Raffini ending nerve receptors (R) arrow) Ruffini endings display dendritic ramifications with expanded terminal buttons
Note the free nerve endings (double arrows)
Note the elongated structure similar to Golgi tendon organ (G) near Conecting With Pacinian corpuscle and Raffini corpuscle
Gordon and Sweet Silver impregnation x1000

Synovial membrane SM: (Figs. 6-9) and (Tables 1-5)

Histological examination of TS serial sections of part of the synovial membrane SM of full term human:(33-36 weeks) CRL 31-34cm) stained by Gordon and Sweet silver impregnation showed the presence of free nerve endings (FNE) and plexus of nerves around a blood vessel, Meissner-like Corpuscle was seen near the blood vessel. The Pacini Corpuscles in the synovial membrane had smaller size than Pacini Corpuscles in the cruciate ligament parenchyma. Pacini corpuscles were seen formed in a botryoidal cluster more than one (Fig 6)

Many encapsulated structures resemble Meissners endings with more than one axon were noted (Fig. 7). Free nerve endings and two large Parisian corpuscles were seen near the blood vessel (Fig. 7)

Fig (8) showed many encapsulated structures resemble Raffini endings displayed dendritic terminal buttons ends

Three Pacini corpusles were near the blood vessel in botryoidal cluster group and conected by a cylinder axon.

There were two Meissner -like Corpuscles, sharing one nerve axon.

Meissensr like structure with nerve ending inside the corpuscles having zigzag arrangement and each branch of the axon was continous wlth the capsule of each corpuscle.

The axon branched into two branches; each branche ran a torsuos way and one terminated in corpuscle as zigzag, and the other terminated in a corpuscle with spiral appearance .Fig

Thjere was also Meissensr like structure with nerve ending having spiral course inside the capsule, giving striate appearance.

Free nerve endings (FNE) round Part of blood vessel were seen.

Many encapsulated structures resemble. Ruffini endings displayed dendritic ramifications with expanded terminal buttons were seen (Fig. 8)

Long, single, big encapsulated structures resembled Golgi stretch tendon organ was seen (Fig (9) composed of outer Capsule .periaxial space surrounded the selender inner capsules and multiple inner large components of sensory terminals that were present in compartments.

Spindle structure with single axon was seen. Free nerve endings (FNE) were noted. Structure similar to Meissner-like Corpuscleswith staite appeatance were noted (Fig. 9)

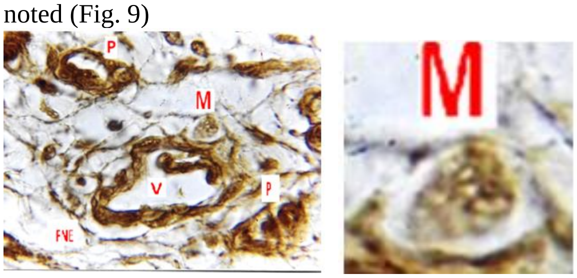


Fig. (6): Photomicrograph of part of TS of part of synovial membrane of full term human :(33-36 weeks) CRL 31-34cm): showing free nerve endings (FNE) and plexus of nerves around blood vessel (V). Pacini in the synovial has smaller size than those in the ligament parenchyma. Pacini corpuscle formed in a botryoidal cluster (P)

Meissner (M) Corpuscle near the blood vessel is seen.
Gordon and Sweet Silver impregnation x1000

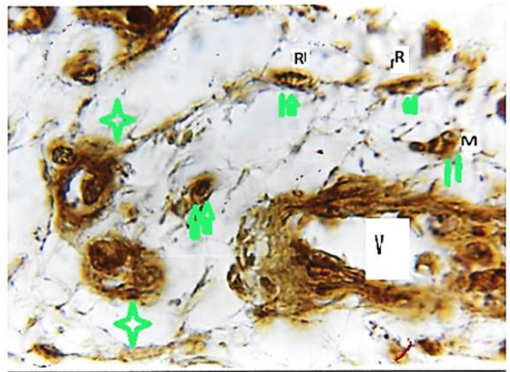


Fig. (7): Photomicrograph of part of TS of part of the synovial membrane of part of full term human:(33-36 weeks) CRL 31-34cm): showing many encapsulated structures resemble Meissners (M)endings with more than one axon(double arrow)

Two large Parisian corpuscles

(Star) are seen near the blood vessel. (V), one axon extended from the capsule.

Note the presence of free nerve endings FNE (arrow)

Gordon and Sweet Silver impregnation x1000

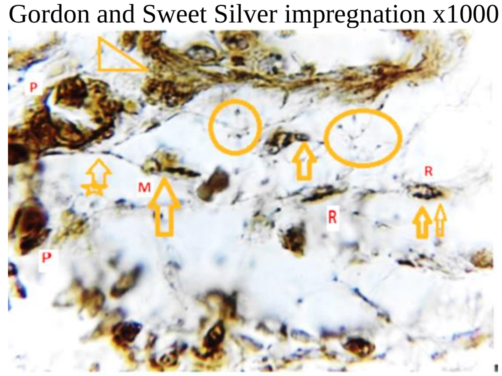


Fig (8): Photomicrograph of part of TS of the synovial membrane of full term human:(33-36 weeks) CRL 31-34cm): showing many encapsulated structures resemble Raffini endings–like structure display dendritic ramifications with expanded terminal buttons ends(double arrow)(R

Note: Pacini corpusle near the blood vessel) is seen in botryoidal (P) head arrow)

Note: Meissensr like structure with nerve ending inside the corpuscles having zigzag arrangement and each branch of the axon is continous wlth the capsule of each corpuscle.

There are two Meissner -like Corpuscles, sharing one nerve axon.(star-arow)

That branches and the branches ran a torsuos way and one terminates in corpuscle as zigzag.

Note: Meissensr like structure with nerve ending has spiral course inside the capsule ,giving striate appearance. (M) (Arrow)

Free nerve endings (FNE) (circle) around Part of blood vessel are seen (V)

Gordon and Sweet Silver impregnation x100

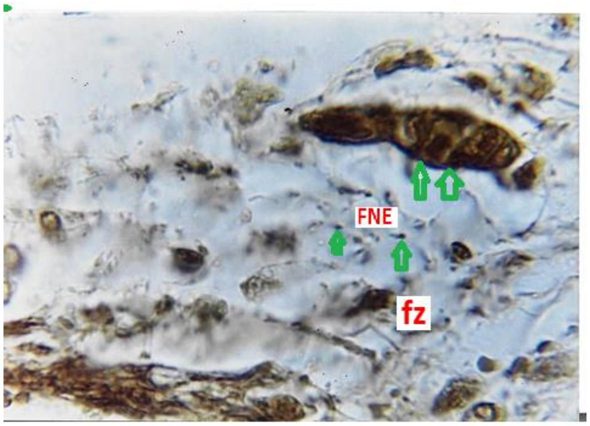


Fig. (9): Photomicrograph of part of TS of part of the synovial membrane of full term human: (33-36 weeks) CRL 31-34cm): showing many long encapsulated structures m similar to Golgi tendon organ .encapsulated (G) double arrow

Note that the tructures resembled Golgi tendon organ, composed of Capsule .periaxial space surrounded the selender inner capsules and multiple inner large components

Note the fusiform (fz) structure with single axon. Note the presence of, many free nerve endings (FNE)

Note the presence of many SPIRAL and ZIGZAG nerve endings similar to Meissner Corpuscle (M) with axon

Gordon and Sweet Silver impregnation x1000

Medial meniscus: (Figs.10-12) and (Tables 1-5)

Histological examination of serial sections stained by Gordon and Sweet silver impregnation of part of T.S of part of medial menisus of 4 month fetus (13-16wks-CRL 9-14cm) showed few free nerve endings between bundles of collagen arranged orthogonally Fig. (10). Meiseners corpuscles were found between the tissue.

Histological examination of serial sections stained by Gordon and Sweet silver impregnation showed that part of TS of part of (Fig11): Photomicrograph of part of medial meniscus of full term human:(33-36 weeks CRL 31-34cm) showed part of Many Meissner corpuscles were seen.Each corpuscle was ovoid in shape and consisted of a stack of modified flattened Schwann cells arranged transversely across the long axis of the corpuscle. The corpuscle was enclosed by a capsule of connective tissue that was continuous with the endoneurium of the nerves that entered it.

Free nerve endings (FNE) in the space around the blood vessel of and orthogonally arranged collagen bundles stained in light brown, and the fibroblasts were dyed stronger brown (Fig. 12)

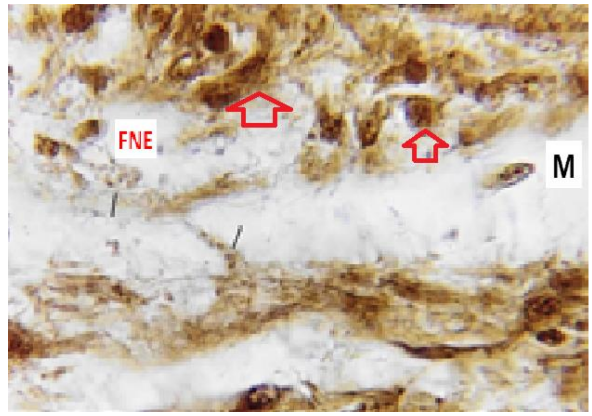


Fig. (10): Photomicrograph of part of T.S of part of medial menisus of 4 month fetus (13-16wks-CRL 9-14cm) showing few free nerve endings between bundles of collagen arranged orthogonally.

Note the Meiseners corpuscle (M) and other structures (arrow)

Gordon and Sweet Silver impregnation x1000

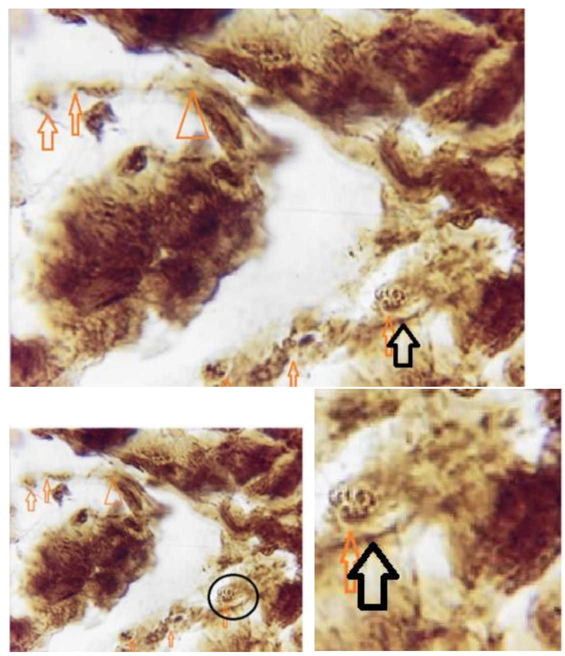


Fig. (11): Photomicrograph of part of TS of part of medial meniscus of full term human:(33-36 weeks) CRL 31-34cm): showing Meissner s (arrow)corpuscles .Each corpuscle Is ovoid in shape and consisted of a stack of modified flattened Schwann cells arranged transversely across the long axis of the corpuscle. The corpuscle is enclosed by a capsule of connective tissue that Is continuous with the endoneurium of the nerves that entered it.

Gordon and Sweet Silver impregnation x1000

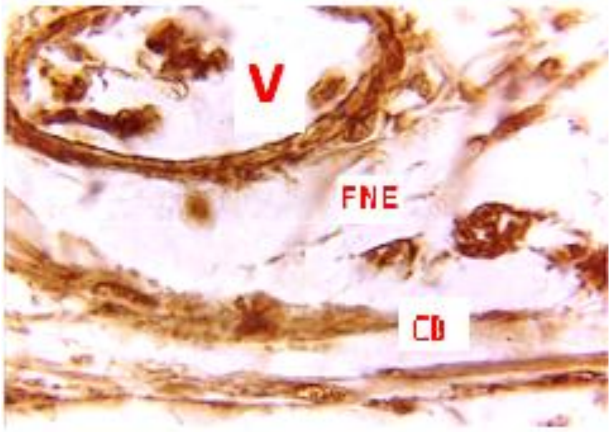


Fig. (12): Photomicrograph of part of TS of part of the medial meniscus of full term human: :(33-36 weeks) CRL 31-34cm):
Showing part of blood vessel and orthogonally arranged collagen bundles stained in light brown, and the fibroblasts were dyed stronger brown.
(CB)(Arrow) and Note the free nerve endings (FNE) in the space around the blood vessel (v)
Gordon and Sweet Silver impregnation x1000

Table(1) : Some histological observations on the developing prenatal neuro- mechano -receptors in the anterior cruciate ligament ACL, synovial membrane SM, and medial meniscusMM of full term fetus of the human knee joint –Based on the present study .

Neuroreceptors	Function in the structures in the prenatal hman knee joint,as leterature	anterior cruciate ligament ACL,	synovial membrane SM,	
Ruffini end organs corpuscles with ramifications,expanded terminals and button ends	stretch	Present	Present	Present
Pacinian corpuscles with CTcapsule and lamellate cells arrangement around a core having onion-cut like appearance	Vibration and tone	Large predominated ,more than the other neuro receptors in ACL	Smaller in size than those of Pacinian corpuscle around blood vessels present in groups ,more than one	NOT NOTED in the present work ,although reported in literature
Meissner Corpuscle with ovoid striated OR zigzaz or spiral appearance of the internal end neuron in the corpuscle	Fine touch, discimination	Present with spiral appearance of the internal end neuron in the corpuscle	Present with zigzaz internal end neuron in the corpuscle and having two axons Near blood vessels	Present with open apex and striated appearance ,although not reported in literature
spray like structures and varicosities end structures	May involve in?musular system contro	Present	Not Present	Present Not
spindle –like structures with one axon	May involve in mechanokanimatic	Present	Present	Present
Flower like structure	May involve in?musular system control	Present	Not	Not
free nerve endings	Nociception – involved in pain convay and modulation as reported in literature-pressure – hot-cold temperature	Present	Present	Present

Table (2): Illustrating the results of the present work after histological examination of serial sections of parts of TS of the anterior cruciate LigamentACL, synovial membrane SM and medial meniscus MMof the prenatal developing human4 month fetus(13-16wks-CRL 9-14cm) and full term human:(33-36 weeks) (CRL 31-34cm)

Type of Receptor	Location	Stimulus Mechanoreceptor	Sensory Modality and threshold	Adaptability	Fibers
(Type 4) Free nerve endings	Anterior cruciate Ligament, synovial membrane, medial meniscus	+ve	pain receptors touch, pressure, heat, cold (nociceptive axon Standring et al., 2016)	Rapid Fast, slow, crude?	A Delta C
Meissner Corpuscle Not mentioned in the literature	Anterior cruciate Ligament, synovial membrane, medial meniscus	+ve	touch,	Rapid	A beta
(Type 2) Pacinian corpuscles	Anterior cruciate Ligament, synovial membrane	+ve	low threshold: vibration	rapidly adapting mechanoreceptors	A beta
(Type 1); Ruffini Corpuscle endings	Anterior cruciate Ligament, synovial membrane	+ve	low threshold, stretch rapid movement and vibration, Standring et al. (2016)	slow adapting mechanoreceptors - adapt rapidly both types of receptors registered the speed and direction of movement Standring et al. (2016)	A beta
Golgi organs, characterized by their poor association with blood vessels.	Anterior cruciate Ligament	+ve	high threshold Compression, muscle tension, stretch. stereognosis. i.e. recognition of shape of held objects (Standring et al., 2016)	Slowly adapting mechanoreceptors (Type 3). Fast	A alpha

Table (3): Classification and comparison of receptor types mentioned in Snell SR2010:Clinical neuroanatomy -7th edition,Wolters Kluwer / Lippincott William & W ilkins and Splittgerber (2019): Snell's Clinical neuroanatomy -8th edition, Wolters Kluwer

Type of Receptor	Location	Stimulus	Sensory Modality	Adaptability	Fibers
free nerve endings are	Cornea, gut, dermis, epidermid, joint, ligaments capsules, bone, dental pulp	Mechanoreceptor	pain fast pain slow touch crude, pressure, heat, cold	rapid	A C delta
Merkel discs hair folicle receptor	Hairless skin Hairy skin	Mechanoreceptor	Touch	slow rapid	A Beta A Beta
Meissner Corpuscles	Dermal papillae of skin of palm and sole of the foot	Mechanoreceptor	Touch	rapid	A Beta
Pacinian corpuscles	Dermis, joint capsules, ligaments, peritoneum, external genitalia .etc	Mechanoreceptor	vibration	rapid	A Beta
Ruffini Corpuscles endings	Dermis of Hairy skin	Mechanoreceptor	stretch	slow	A Beta
Neuromuscular s spindles	Skeletal muscles	Mechanoreceptor	Stretch Muscule length	fast	Aalpha A Beta
Neurotendenous spindles	tendons	Mechanoreceptor	Stretch comprssion muscle tension	fast	Aalpha

Table (4): According to Snell (2010) and Splittgerber (2019) who mentioned that in Joint receptors, four types of sensory receptors could be located in the capsule and ligaments of synovial joints. Three of those endings were encapsulated and resembled pacinian, Ruffini, and tendon stretch receptors. They provided the central nervous system with information regarding the position and movement of the joint .A fourth type of ending was non encapsulated and was thought to be sensitive to excessive movement and transmit pain sensations.

Morphology:Encapsulated Joint receptors resembled	Function :information regarding
Pacinian	position and movement of the joint
Ruffini,	tone
tendon stretch receptors	stretch
non encapsulated ending	transmit pain sensations.

Table (5): Type of receptor in articular joint present in the present study according to Standring et al. (2016)

Type of receptor in joint	Modality and response	Function mediation
Raffini endings	adapt rapidly respond to rapid movement and vibration	speed and direction of movement
lamellated articular corpuscles	rapid movement and vibration responded to rapid movement and vibration, adapt rapidly	registered the speed and direction of movement
Golgi tendon organs	Slow to adapt.	they mediated position sense and also stereognosis .i.e.recognition of shape of held objects
Simple endings attachmed to the capsule and ligaments	.nociceptive	pain

Discussion:

In the present study , silver impregnatin-Gordon and sweet stain method was chosen to illustrate the neuronal end recepors and the free nerve endings in the anterior cruciate ligament ACL,synovial membrane SM, and medial meniscus MM of prenatal developing human knee joint ,becuase the silver impregnation technique was documented historically to preserve the fine detail of nerves and selectively illustrated myelinated and unmyelinated neuritis.

That agreed with Castano et al.,1995 who pointed that, the silver impregnation technique was historically recommended for staining of peripheral nerve endings, including Meissner corpuscles. The silver impregnation method could selectively demonstrate both unmyelinated and myelinated neurites and preserve the fine detail of nerves.

However, Meghan et al. (2022) in their illusration of Meissner corpuscles mentioned that in the silver impregnation technique, tissue samples were fixed in neutral or simple formalin or Bouin solution. Frozen sections were cut into thin sections and placed into the impregnating solution composed of urea, 1% silver nitrate, 95% ethyl alcohol, pyridine, 1% mercuric cyanide, and 1% picric acid in distilled water. After incubation for 5.5 hours, the specimens were submerged in a solution of 1% hydroquinone, 5% anhydrous sodium sulfate, and urea, followed by a mixture of 0.2% gold chloride and glacial acetic acid, then 5% sodium hyposulfite. After immunofluorescent staining, specimens were viewed using confocal scanning laser microscopythere

Meghan et al. (2022) pointed that, there were new advanced techniques to illustrate the nerve endings: Two-photon excitation microscopy was a novel fluorescence imaging technique enabling high-resolution visualization of living tissue near the skin surface, including Meissner corpuscles. Pham et al. (2016) mentioned Two-photon microscopy utilized the long-lasting lipophilic fluorescent dye carbocyanine DiOC (3) and 484 nm laser for live imaging of the axonal components of the corpuscles. The persistence of the dye for several weeks allowed for the ability to image the corpuscular neurites in vivo over a prolonged period to evaluate the mechanical response and structural changes of the corpuscles. A limitation of that visualization method was the inability to highlight other components of the receptors, such as the collagenous capsule or Schwann cells.

Meghan et al. (2022) added that the immunohistochemical staining targeting differential antigenic expression could distinguish between the neural and supportive components of Meissner corpuscles as Vega et al. (1996) reported that double immunolabelling with monoclonal antibodies against human neurofilament proteins (NFP) and S100 could reliably stain the central axon and Schwann cells, respectively.

Meghan et al. (2022) mentioned that other immunohistochemical stains for the central axon included neuron-specific enolase, protein gene product

9.5, neurocalcin, and neurofilament subunits. Substance P, calcitonin gene-related peptide, and gamma-melanocyte stimulating hormone had also been utilized to stain the neuronal components of Meissner corpuscles. Lamellar cells were identifiable by using stains targeting the receptor for the vimentin and growth factor receptor TrkB.

In the present work ,histological examination of serial sections stained by silver impregnation-Gordon and Sweet method of parts of TS of anterior cruciate ligament ACL and the synovial membrane SM of full term human knee joint (33-36 weeks) CRL 31-34cm), showed that the ACL had neuronal structures in the form of spindle like structures with one axon , Meissener like corpuscle with spiral nerve endings appearance of the encapsuled nerve ending . Large single Golgi like organ, with large encapsulate components. Free nerve endings and Bundles of nerve fibers, besides plexus of nerves were noted near spray like structures Bundels of nerves arranged in one row before and behind the spray structure were observed. Ruffini like endings displayed dendritic ramifications with expanded terminal axon and terminal buttons ends were found. A structure similar to flower was seen. Large Pacinian corpuscles were noted, each corpuscle was formed of layers of cells arranged in lamellae darkly stained around a central core, and the capsule of Pacinian corpuscle was continuous with the endoneurium of the afferent nerve. Some Pacinian corpuscles simulated cut onion structure; other Pacinian corpuscles were elongated and were similar to a broom. Pacinian corpuscles occupied a large surface area of the ACL of the full term prenatal fetus. Pacinian corpuscle of ACL were single and larger in size than Pacinian corpuscle of the synovial membrane SM that were present in groups around blood vessels.

In the present work ,histological examination of serial sections stained by silver impregnation -Gordon and Sweet method of parts of TS of anterior cruciate ligament ACL , showed the presence of Ruffini nerve ending like receptors ,whith dendritic ramifications and expanded terminal axon and terminal buttons ends.. Lamellar Schwann cells associated the Raffini corpuscle like endings. Finger-like projections called axonal spines or microspikes, extend into the surrounding tissue from Ruffini endings were seen.

The Ruffini –like endings seen in the anterior cruciate ligament ACLof the prenatal developing full term human knee joint:(33-36 weeks) CRL 31-34cm were mechanoreceptor.They might have a role similar to the Ruffini –like endings in the periodontal ligament, which were responding to mechanical stimuli and interfered with regeneration/development processes of nerves as they had proved to have potential for neuroplasticity in the periodontal ligament in tooth eruption??Besides the involvement of the Ruffini ending in the tone and stretch in the articular structure of the synovial joints. The function of Ruffini –like ending of theACL of the prenatal developing human knee joint needed more researches to confirm the anatomical function of Raffini mechanoreceptors in the developing prenatal human ACL in the knee joint.

The results of the present study were similar to. Toyoma1985 who studied the ultrastructural, histochemical and morphology of sensory corpuscles in the capsule- in the cat elbow joint. He found by light and electron microscopy, two types of corpuscles: sensory corpuscles; Pacini-type and Ruffini-type corpuscles. Silver impregnation revealed a single straight axon terminal in Pacini-type and highly-ramified fine axons in Ruffini-type corpuscles. Pacini-type corpuscles, were 100-200 microns long and 30 microns wide, consisted of dense lamellae of lamellar cells and thick capsule. The lamellar portion contained a centrally-located axon terminal, and was similar in organization to the inner core of the typical Pacini corpuscle. The capsule was the continuation of perineurial sheath. That corpuscle was devoid of outer core structure as seen in a typical Pacini corpuscle. Ruffini-type corpuscles, 50-150 microns long and 25-50 microns wide, had the branched axon terminals with varicosities under the incomplete capsule. Axons, which were surrounded by thin Schwann cell processes, were embedded in the dense layers of collagen fibrils. The interior of the corpuscle was separated into small compartments by cell processes extended from the capsule. The axon varicosities contained numerous mitochondria. Those fine structures of the corpuscles were similar to those of Ruffini corpuscles reported so far in other regions. Both Pacini-type and Ruffini-type corpuscles were clearly demonstrated by histochemistry for ChE. In as much as the staining feature of corpuscles was different from each other, the distribution pattern of corpuscles in the joint capsules could be obtained by examining semi-serial sections. Pacini-type corpuscles were mainly found in the synovial layer, while Ruffini-type corpuscles were mainly located in the fibrous layer of the joint capsule. Both types of corpuscles were located near the median nerve on the flexor side of the joint. The reaction products of ChE activity were located in the peri-axonal as well as inter-lamellar spaces of Pacini-type corpuscles, and in the peri-axonal region as well as around Schwann cell processes of Ruffini-type corpuscles. No definite reaction product was found within axon terminals. Some reaction products were also found in the rough endoplasmic reticulum and/or nuclear envelope, suggesting that ChE was synthesized by Schwann cells. The significance of those sensory corpuscles with regard to the deep sensation in the joint capsule was discussed from their point of view of the electro-physiological characteristics of the corpuscles

The results of the present study were similar to Maeda et al., 1999 who studied the Ruffini ending as the primary mechanoreceptor in the periodontal ligament.They mentioned that the periodontal ligament received a rich sensory nerve supply and contained many nociceptors and mechanoreceptors. Although its various kinds of mechanoreceptors had been reported in the past, only recently had studies revealed that the Ruffini endings--categorized as low-threshold, slowly adapting, type II mechanoreceptors--were the primary mechanoreceptors in the periodontal ligament. The y reported that periodontal Ruffini endings displayed dendritic ramifications with expanded terminal buttons and, furthermore, were ultrastructurally characterized by expanded axon terminals filled with many mitochondria and by an association with terminal or lamellar Schwann cells. The axon terminals of the periodontal Ruffini endings had finger-like projections called axonal spines or microspikes, which extend into the surrounding tissue to detect the deformation of collagen fibers. The functional basis of the periodontal Ruffini endings had been analyzed by histochemical techniques. Histochemically, the axon terminals were reactive for cytochrome oxidase activity, and the terminal Schwann cells had both non-specific cholinesterase and acid phosphatase activity. On the other hand, many investigations had suggested that the Ruffini endings had a high potential for neuroplasticity. For example, immunoreactivity for p75-NGFR (low-affinity nerve growth factor receptor) and GAP-43 (growth-associated protein-43), both of which played important roles in nerve regeneration/development processes, had been reported in the periodontal Ruffini endings, even in adult animals (though these proteins were usually repressed or down-regulated in mature neurons). Furthermore, in experimental studies on nerve injury to the inferior alveolar nerve, the degeneration of Ruffini endings took place immediately after nerve injury, with regeneration beginning from 3 to 5 days later, and the distribution and terminal morphology returning to almost normal at around 14 days. During regeneration, some regenerating Ruffini endings expressed neuropeptide Y, which was rarely observed in normal animals. امم مثالكم- سورة الانعام 38On the other hand, the periodontal Ruffini endings showed stage-specific configurations which were closely related to tooth eruption and the addition of occlusal forces to the tooth during postnatal development, suggesting that mechanical stimuli due to tooth eruption and occlusion were a prerequisite for the differentiation and maturation of the periodontal Ruffini endings. Further investigations were needed to clarify the involvement of growth factors in the molecular mechanisms of the development and regeneration processes of the Ruffini endings.

In the present study histological examination of serial sections stained by Gordon and Sweet,silver imprignaion technique of parts of TS of ACL,SM ,and MM of full term 33-36 weeks) CRL 31-34cm)of the prenatal developing human knee joint showed the presence of encapsulated neural ends structures ,besides free nerve endingsFNE.These neural ends structures were in ACL and SM: Pacinian corpuscles, Raffini end like organs, Meissner Corpuscle, Golgi tendon organ. In ACL, additional strange flower like structure ,spray like structure,and spindle structures with one axon were noted.

Pacinian corpuscles had lamellate cells around a central core, and the CT capsule of the corpuscle was continous with the endoneurium of the nerve. Pacinian corpuscles were the dominated structure in ACL,They had onion cut or broom like appearance.The size of Pacini corpuscles was smaller in SM, and were found in groups near the blood vessels.

Ruffini end like encapsulated structure ,with ramification and expanded terminals and button ends,were noted in ACLand in SM.

Meissner Corpuscles of full term 33-36 weeks) CRL 31-34cm) of the prenatal developing human knee joint were noted in MMand was not reported before in the literature.

Meissner like Corpuscles were oval structures with striated or zigzag appearance due to the toutrous course of the nerve ending in the corpuscle.They were noted in ACL,SM,and MM of the full term fetus of the prenatal developing human knee joint. Two Meissner -like Corpuscles, sharing one branched nerve axon in the SM were noted. The nerve endings of the branched axon ran a torsuos way in one corpuscle and one terminated in the corpuscle as zigzag.

The results if the present study were similar to Meghan etal., 2022 who explained that cutaneous Meissner corpuscles were found in glabrous skin, particularly the fingertips, palms, and soles of feet, lips, palate, tongue, and genitalia. enhancing the sensitivity of these tissues to light touch. The density of Meissner corpuscles varied between studies .They pointed that ,structures morphologically identical to Meissner corpuscles were identified in abnormal locations had been termed tactile corpuscle-like bodies, Wagner-Meissner bodies, pseudo-Meissner corpuscles, and Meissner-oid corpuscles. Several cases had been published detailing the identification of proliferation of these Meissner corpuscle-like structures within the lamina propria, the gastrointestinal mucosa, including the esophagus, stomach, and colorectum.

Meghan etal., 2022pionted that Meissner corpuscles were Clinically highly Significant in reading of Braille.Meissner corpuscles had integral aspect of the human sensory system, as they were required for discriminatory touch and grip control. The high sensitivity of these receptors also allowed for the reading of Braille using the fingertips بلي سورة القيامة4 قَادرين علي أن نسوي بنانه. Males and females had a similar number of corpuscles in each digit, although, given the larger average surface area of male hand and fingers, men had a lower density of receptors which might contribute to a small difference in touch receptivity ليس الذكر كالأنثي – ال عمران36 عمران. Dillon et al., 2001 .The size, density, and complexity of Meissner corpuscles also declined significantly with increasing age. [.Iwasaki et al., 2003] Animal studies had revealed that with increasing age, the neurites يس من نعمره ننكسه في الخلق 68يسsupplying Meissner corpuscles became progressively more coarse, tortuous, and varicose with the disintegration of lamellar processes.[Nava et al., 1996] Older neurites demonstrated less parallel orientation and an increased number of axonal bifurcations per corpuscle.[Mathewson and Nava 1985] These findings might underlie the age-related decrease in touch sensitivity.

Big ,oval,single Golgi tendon organ –like with periaxial space and large components and sensory terminals in a inner capsule were noted in ACL and SM. Of the full term fetus of the prenatal developing human knee joint. Golgi tendon organ –like was the largest component in the SM among the other neuroreceptor noted.

In the present study ,the Spray like structures were found in the ACL ,but were not seen in SM or MM of the prenatal developing human knee joint. .Spindle structures with one axon were noted in ACL,SM and MM.These neural structures had occupied large surface area in the ACL,SM,but had small representation in MM of the full term fetus in the prenatal developing human knee joint.These neuronal elements could provide the central nervous system CNS with information about noxious stimuli, chemical events , mechanical changes ,orientation,vibration,steriognosis,movements and position-related stretches of the ACL ligaments.SM, and MM ,thus could influence the skeletomotor system in the prenatal developing human knee joints.Many authors referred to these neuronal structures as (neuro-mechano receptors) Zimny, Schutte, and Dabezies(1986). Wu et al. (2015). However no authors had described Meissner like Corpuscle in the prenatal ACL, SM, and MM.

The results of the present study agreed with Schutte et al. (1984) who found in human cruciate ligaments fusiform mechanoreceptors structures measuring 200 by seventy five micrometers with a single axon exiting from the capsule of the in adult human cruciate ligament .

In the present study histological examination of serial sections stained by Gordon and Sweet,silver imprignaion technique of parts of TSof parts of the ACL and SM of full term 33-36 weeks) CRL 31-34cm)of the prenatal developing muman knee joint , showed the presence of Pacinian corpuscles, but Pacinian corpuscles were not noted in MM. That Pacinian corpuscles had a large size in ACL ,and small size in SM and were found in groups near blood vessels in SM. Pacinian corpuscle had a CT capsule ,and lamellate cells around a central core giving the appearance of cut onion or a boom. The capsule of Pacinian corpuscle was continues with the endoneurium of the afferent nerve. Pacinian corpuscles were the largest neural element among the other neuronal end structures of ACL of the full term fetus in the developing prenatal human knee. The presence Pacinian corpuscle of in groups in SM more than one indicate d momentary functional response to stimuli.

The results of the present study agreed with Zimny, Schutte, and Dabezies(1986) who memtioned that Ruffini end organs and Pacinian corpuscles were mechanoreceptors found the ACL human knee joint. Their preliminary morphometric analysis showed that the mechanoreceptors were greater at the femoral and tibial ends of the ligament and constituted approximately 2.5% of the ligament. They concluded that the human ACL had the anatomic basis for a discriminating afferent outflow to the central nervous system.

The results of the present study coincided with Schutte et al. (1987) who identified in the anterior cruciate ligament, in human cadavers, besides the free nerve endings, Raffini and Pacinian corpuscles. They mentioned that those neural elements comprised one per cent of the area of anterior cruciate ligament.

The results of the present stud agreed with Johansson et al. (1991) who reviewed the morphologic, physiologic, and clinical evidence for the sensory role of the cruciate ligaments. They concluded that, the sensory system of the cruciate ligaments was significantly contributed to the functional stability of the knee joint by preprogramming of the muscular stiffness around the knee joint and thereby of the knee joint stiffness.They found that the cruciate ligaments accommodated morphologically different sensory nerve endings : They mentioned that (Ruffini endings, Pacinian corpuscles, Golgi tendon organ like endings, and free nerve endings) were noted with different capabilities of providing the central nervous system with information not only about noxious and chemical events but also about characteristics of movements and position-related stretches of those ligaments. They mentioned that their survey of the available data revealed that low threshold joint-ligament receptor (i.e., mechanoreceptor) afferents evoked only weak and rare effects in skeletomotor neurons (alpha-motor neurons), while they frequently and powerfully influenced fusimotor neurons (gamma-motor neurons). The effects on the gamma-muscle-spindle system in the muscles around the knee were so potent that even stretches of the cruciate ligaments at relatively moderate loads (not noxious) might induce major changes in responses of the muscle spindle afferents. As the activity in the primary muscle spindle afferents modified the stiffness in the muscles, the cruciate ligament receptors, via the gamma-muscle-spindle system, might participate in the regulation and preprogramming of the muscular stiffness around the knee joint and thereby of the knee joint stiffness.

The results of the present stud agreed with Zimny , and Wink (1991) who mentioned that Ruffini mechanoreceptors were believed to contribute mainly to maintenance of muscle tone, Pacinian corpuscles and Golgi tendon organs were stimulated during movement, and free nerve endings were nociceptors. Thus, receptors of the knee joint were able to produce a discriminating afferent inflow to the central nervous system (CNS), thereby contributing to the protection and function of the joint through the musculature. Ruffini endings, Pacinian corpuscles, and free nerve endings were most prevalent in the fibrous joint capsule; Golgi tendon organs were most common in the collateral and cruciate ligaments and the menisci. In the anterior and posterior cruciate ligaments (ACL, PCL), receptors were concentrated at the tibial and femoral attachments of the ligaments. In the menisci, neural elements penetrate the horns and the outer and middle thirds of the body.

The results`of the present study were similar to Wu et al. (2015) who studied the mechanoreceptors in collateral ligaments of the human ankle joint. Wu et al. (2015) reported that lateral ankle sprain (LAS) and chronic ankle instability (CAI) were becoming a hot spot in the sports medicine and orthopedics research. Their study focused on the morphological structure and distribution of the proprioceptive mechanoreceptors in the lateral ligaments of the human ankle. They used Gold-chloride staining after paraffin sectioning. They aimed to provide some morphological evidence for the clinical treatment of the LAS and CAI.They analyzed the pattern and types of sensory nerve endings in ankle collateral ligaments using histological techniques, in order to observe the morphology and distribution of mechanoreceptors in the collateral ligaments of cadaver ankle joint,and to provide the morphological evidence for the role of the ligament in joint sensory function . They used twelve lateral collateral ligaments including anterior talofibular ligament (ATFL; n = 6), posterior talofibular ligament (PTFL; n = 6), and calcaneofibular ligament (CFL; n = 6. were harvested from six fresh frozen cadavers. The ligaments were embedded in paraffin, sectioned at 4 μm, and then stained using a modified gold-chloride staining methods. They divided the collateral ligament into three segments: proximal, middle, and distal segments.They analyzed Fifty-four ATFL slides, 90 PTFL slides, and 108 CFL slides. They classified the Mechanoreceptors based on Freemen and Wyke's classification. Mechanoreceptor distribution was analyzed statistically. One-way ANOVA (postHoc LSD) was used for statistical analysis. They identified four typical types of mechanoreceptors in the collateral ligaments of the human ankle. All the four typical types of nerve endings (the Ruffini corpuscles, Pacinian corpuscles, Golgi tendon organs, and free nerve endings) were identified in those ligaments. Pacinian corpuscles were the predominant in all four complexes. More mechanoreceptors were found in synovial membrane near both ends of the ligaments attached to the bone. They did not find statistical differences in the amount of mechanoreceptors among distal, middle, and proximal parts of the ligaments.. Pacinian corpuscles were the predominant in all four receptors. That indicated that the main function of ankle collateral ligaments was to sense joint speeds in motions. They found that Pacinian corpuscles were the most common mechanoreceptors in all the ankle collateral ligaments. Pacini corpuscle formed in a botryoidal cluster, paralleling to long axis of ligaments.

The results of the present study agreed with Banios, et al. (2022) who reviewed the anterior and posterior Cruciate Ligaments Mechanoreceptors: and mentioned that Schultz et al. (1984) demonstrate for the first time the histology of MRCs in human cruciate ligaments (using gold-chloride staining techniques), taken at the time of amputation or autopsy They found 1–3 Golgi organs in each ligament, located at the surface of each ligament beneath the synovial membrane.

Zimny et al.1986 presented for the first-time a histology of two morphologically distinct MRCs in the human ACL, and identified Ruffini and Pacinian corpuscles in 6 human subjects

The results of the present study coincided with Krauspe et al. 1995 who used an immunocytochemical approach to identify nerve fibers and corpuscular endings, involving a monoclonal antibody directed against the 68-kDa neurofilament protein, found two types of corpuscular-like endings; “spiral-like” (type I) and “spray-like” (type II) endings in a child’s ACL mostly near its bony attachment. Adachi et al.(2002) analyzed the changes of MRCs in the ruptured ACL remnants of 29 patients by gold chloride staining and reported that the MRCs in the ligament remnants could persist for a long time following an injury . They found MRCs in all ACL remnants, most commonly subsynovially or on the superficial layer of the ligament. The median total number of MRCs in an ACL remnant was 18 (range 8–30), and the median density of mechanoreceptors was 25 (range 12–69)/g.

The results of the present study came with Lee et al. 2009 who identified(8 Ruffini, 11 Golgi) MRCs in two normal ACLs from healthy knees at both tibial and femoral attachments,after harvesing 36 tibial remnants during ACL reconstruction and 2 normal ACLs .They found MRCs in 12 out of 36 cases, (33%), with a total of 17 MRCs (6 Ruffini and 11 Golgi) were observed, the presence of Ruffini and Golgi at the tibial remnant of the ruptured ACLs and normal ACL substance was verified.

The results of the present study were similar and coincided with Dhillon et al. (2010); Dhillon et al. (2010), Gao et al. (2016); Çabuk and Çabuk (2016) in adition to Li et al. (2018)

Dhillon et al. (2010) evaluated the proprioceptive structures in residual ACL remnants using immunohistological methods. They used hemotoxin and eosin stains, and monoclonal antibodies to S-100 and NFP to evaluate 63 ACLbiopsies from stumps. They noted morphologically normal mechanoreceptors MRCs: Ruffini corpuscles, Pacinian corpuscles and Golgi-like organs were identified, in 46% and 52.4% of stumps, respectively. Mostly located subsynovially,

Sonnery-Cottet et al. 2014 studied the histology of the remaining tissues of 26 partial ACL tears. Immunohistochemical studies revealed many free nerve endings and few Ruffini and Golgi corpuscles.

The results of the present study were partly similar and in accordance with Gao et al. 2016 as they did not find Pacini corpuscles in ACL,and Pacini corpuscles were noted in the present study in ACL of the full term of the prenatal developing human knee , in histological sections stained by Gordon and sweet silver impregnation. Gao et al. 2016 in their study, obseved the morphology and quantity of mechanoreceptors MRCs in the remnant stumps of 40 injured ACLs using immunohistochemical methods .They found Ruffini corpuscles, Pacinian corpuscles, Golgi-like tendon organs, and free nerve endings in most of the ACL stump specimens examined in that study. analysed quantitatively the mechanoreceptors MRCs 4 tendons and 4 ligaments from 8 fresh frozen cadaveric knees using hematoxylin–eosin staining and immunohistochemistry (S100 immunostaining) . They noted that, free nerve endings were the predominant ones, followed by Ruffini and Golgi-like endings. No Pacini corpuscles were found. MRCs were located mostly near the bone insertions of the cruciate ligaments.

In the present study histological examination of serialTS sections of parts of ACL of full term prenatal developing human knee,showed the presence of Ruffini corpuscles, Pacinian corpuscles, Golgi-like tendon organs, and atypical MRC ,That was similar to.. Li et al. 2018, who observed the changes in the quantity and morphology of MRCs in different-state remnant stumps of 57 ruptured ACLs . A total of 2365 sections were subjected to immunofluorescence staining.They found 147 Ruffini corpuscles, 40 Pacinian corpuscles, 8 Golgi-like tendon organs, and 58 atypical MRCs in all ligament specimens . Free nerve endings were also observed.

The results of the present work were partly similar to Schenk , Spaethe, Halata1996 who studied the ultrastructure and distribution patterns of sensory nerve endings in the dorsal knee joint capsules of the beagle dog (Canis familiaris) using light and electron microscopy. They found different sized Ruffini corpuscles: very small, small, medium.large. Ruffini c they divided each dorsal knee joint capsule into four quadrants, cut into small pieces and then processed for electron microscopy. Free nerve endings and corpuscular nerve endings (Ruffini and lamellated corpuscles) were found. They were most frequently observed in the medial-proximal quadrant of the dorsal joint capsule. All nerve endings were found to be situated within or adjacent to the fibrous layer of the capsule. No nerve endings were found within the synovial layer. Free nerve endings were usually situated at the border between the fibrous layer and the synovial layer near blood vessels. Their associated afferent axon was myelinated (1.5-2.5 microns in diameter) or non-myelinated (0.3-1.5 microns in diameter). Ruffini corpuscles were found in the fibrous layer and within the dorsal ligamentous apparatus. Each Ruffini corpuscle was surrounded by a multilayered perineural capsule which was usually incompletely developed. The perineural capsule was the continuation of the perineurium of the afferent axon and gave a cylindrical form to the corpuscles. Ruffini corpuscles were present as single, cylindrical structures (small corpuscles) or as aggregates of these cylinders (large corpuscles). Both varieties consisted of terminal nerve endings surrounded by collagen fibres which passed through the opened ends of the cylinders. The diameter and length of the small Ruffini corpuscles were 80 microns and 400 microns, as compared to 200 microns and 800 microns for the large aggregated forms. The supplying afferent axons of both types were 4-5 microns in diameter. Two types of small lamellated corpuscles could be observed in the fibrous layer: very small corpuscles, 55 microns long, 25 microns wide and medium corpuscles, 100 microns long, 40 microns wide. Each consisted of an inner core of terminal Schwann cells, a nerve terminal and a perineural capsule. Some lamellated corpuscles had two inner cores and two nerve terminals. The diameter of the afferent axon was approximately 6 microns.however They mentioned that Vater-Pacini corpuscles were not found in the dorsal knee joint capsule of the dog

Messieners like corpuscles in ACL , SM and MM of the prenatal developing human knee joint

In the present study histological examination with light microscope of serial sections of parts of ACL ,SM and MM of full term fetus of the prenatal developing human knee joint showed the presence of Messieners corpuscles with variable orientation ,some corpuscles had stacked flat lamellate cells giving the appearance of striate corpuscle in MM of full term fetus,frequently the nerve ending ran a toursous way in the corpuscle giving a zigzag appearance of the corpuscle in the SM of full term fetus. Messieners corpuscles in MM had a capsule that was incomplete at its apex with open upper end and was perpendicular in the tissue.

The results of the present work agreed with Snell: 2010 and Splittgerber (2019) who reported that Meissner corpuscle was ovoid in shape consisted of stack of modified Schwan cells arranged transversely across the long axis of the corpuscle .the corpuscle was enclosed in a CT capsule that was continous with the endoneurium of the nerves that entered`it. A few mylinated nerve fibers entered the deep end of the corpuscle, and umylinated decreased in size and ramify among the Schwan cells issner.

The results of the present study were similar to Meghan et al. (2022) who illustrated that under light microscopy, Meissner corpuscles appeared as coiled, spring-like structures composed of stacked, disk-like lamellar cells. The orientation of the lamellae was variable, but they were typically parallel to the skin surface. The Schwann cell-derived lamellar cells had peripherally displaced nuclei and were contained within a fibroblastic capsule that was incomplete at its apex. The neurites that coursed through the lamellae were not visible by traditional hematoxylin and eosin staining techniques.Meissner corpuscles were ellipsoid mechanoreceptors located superficially within the dermal papillae at a depth of approximately 150 micrometers. The corpuscles were approximately 20 to 40 micrometers in diameter and 80 to 150 micrometers in length, with their long axis oriented perpendicularly to the skin surface. Vega et al. (2012) one corpuscle might be found within every two to four dermal papillae, with less than three corpuscles per papilla. Both the size and density of the receptors depended on the site of origin.

Meghan et al. (2022) pointed that each corpuscle was comprised of three primary components: elongated Schwann cells, a connective tissue capsule, and a central axon.CAUNA et al. (1960). The flattened Schwann cells were organized in a stacked conformation in a background of an interlamellar matrix composed largely of collagen and microfilaments (Vega et al., 2009). The capsule of Meissner corpuscles was derived from the endoneurial-perineural fibroblastic connective tissue. The deeper aspect of the corpuscle was lined by two to four layers of fibroblasts and fibrillary matrix. The apex of the capsule was incomplete. In that region, collagen fibrils from the interlamellar matrix extended into the dermis and anchored the receptor to the basal aspect of the epidermis (Meghan et al., 2022).

Meghan et al. (2022) mentioned thar each corpuscle was supplied by a nerve ending derived from an intermediate-large amyloid-beta myelinated afferent fiber Vega et al. (2012).

CAUNA1965 mentioned that, innervation by additional unmyelinated C fibers had also been reported, although these fibers mighty simply pass through the corpuscle to reach the epidermis. CAUNA et al. (1960) pointed that typically, Meissner corpuscles were supplied by a single axon, but corpuscles with 2 to 7 accessory branches from the primary axon had been documented. The nerve fiber retained its myelin sheath as it entered the corpuscle but became amyelinic after a short distance. Vega et al. (2009). The nerve fiber branched multiple times, forming bulbous expansions as it meandered tortuously throughout the lamellae. The cell body of the supplying neuron resided within a dorsal root ganglion or cranial nerve sensory ganglion. A single neuron from the sensory ganglion was capable of supplying multiple corpuscles (Zimmerman et al., 2014).

However Meghan et al. (2022) pionted that Meissner corpuscle played a minor role in human disease. Meissner corpuscles were noted as a benign accessory component in some cellular nevi, schwannomas, and neurofibromas. A single case report described the presence of Meissner-like corpuscles within a mature ovarian cystic teratoma. Occasional case reports described benign tumors composed largely or entirely of Meissner corpuscles known as Wagner-Meissner neurilemmomas (WMNs). WMNs present as slow-growing soft tissue masses involving the deep dermis and subcutaneous tissues. WMNs, had been reported on the cheek, lower extremity, and vulva in an atypical distribution of Meissner corpuscles. Those tumors were typically well-demarcated, residing within a fibrous collagen capsule, although a single case report documented an infiltrative growth pattern. On histological examination, WMNs displayed lamellated complexes composed of up to 20 laminar cells, resembling Meissner corpuscles. Those tumors stained positively for neuron-specific enolase, vimentin, and S100 but lack the nerve fibers that supplied the receptors, differentiating those abnormal structures from the functional corpuscles in the dermis

Meghan et al., 2021pionted that the origin of Meissner corpuscles lesions was unclear but might represent hamartomas, neural neoplasms, or a reactive process. Typically discovered incidentally during colonoscopy, these proliferations often resembled colonic polyps, leading to their biopsy and identification. Pathological examination of those lesions revealed discrete clusters of eosinophilic aggregates within the lamina propria. Those structures were comprised of spindle-shaped cells, each with a single eccentric, oblong nucleus and lamellated, eosinophilic cytoplasm. Staining for S100 was positive while the histiocytic marker CD68 was negative, indicating the Schwannian or neural origin of the lesions. The differential diagnosis of those proliferations included mucosal amyloid deposition and mucosal granulomas, although negative staining for Congo red and CD68, respectively, could be reliably used to differentiate those disorders. The presence of bodies within the gastrointestinal tract was benign.

The results of the present study were similar with Snell (2010) and Splittgerber (2019) who mentioned that encapsulated neuroreceptors showed wide variation in size and shape , and the termination of the nerves was covered by a capsule. Meissner s corpuscles were located in the dermal papillae of the skin, and especially of the palm of the hand and the sole of the foot .Many also were present in the skin of the nipple and external genitalia .Each corpuscle was ovoid in shape and consisted of a stack of modified flattened Schwann cells arranged transversely across the long axis of the corpuscle. The corpuscle was enclosed by a capsule of connective tissue that was continuous with the endoneurium of the nerves that entered it. A few myelinated nerve fibers entered deep end of the corpuscle myelinated and unmyelinated decreased in size and ramify along the Schwann cells. There was considerable reduction in the number of Meissner s corpuscles between birth and old age.68 ومن نعمره ننكسه في الخلق .سورة يس

عنوانPacinian corpuscles ,Raffini end organs and Golgi tendon organ –like structure,and free nerve endingsFNEin the ACL, SMand MM of prenatal developing human knee joint:

In the present study, histological examination of serial sections stained by Gordon and sweet method –silver impregnation of TS of parts of SM of full term prenatal human knee joint, showed the presence of Golgi tendon–like organ, that was single large oval structure and was seen not associated with the blood vessels. Golgi tendon organ,composed of CT Capsule ,periaxial space surrounded the selender inner capsule , and multiple inner large components and sensory terminals The structure that resembeled Golgi tendon organ had the largest size among the types of the neouroreceptors in the SM of full term human knee joint found in the present study . Golgi tendon organ was related to musculature control of the knee joint.

In the present study ,the presence of Pacinian like corpuscles ,Ruffini like end organs , Golgi tendon –like organ and free nerve endings FNE in the anterior cruciate ligament ACL, synovial membrane SM of full term of the prenatal developindg human knee joint indicated sensory function of these neuronal elements in the developing prenatal human anterior cruciate ligament ACL,synovial membrane SMand medial meniscusMM of the prenatal developing human knee joint.

The results of the present study were similar to Freeman and Wyke1967 who classified encapsulated nerve endings in the synovium of the joints of cats as follows : Ruffini endings were low threshold, slow adapting mechanoreceptors (Type 1); Pacinian corpuscles were low threshold, rapidly adapting mechanoreceptors (Type 2); Google organs, characterized by their poor association with blood vessels, were high threshold, slowly adapting mechanoreceptors (Type 3); and free nerve endings are pain receptors (Type 4).

The results of the present study were in agreement with Grönblad et al. (1985); who reported that substance P-immunofluorescent nerves were closely associated with pain transmission and were found in human knee synovial membrane and menisci. Both tissues contained also enkephalin-immunofluorescent nerves, which might be involved in the modulation of pain transmission. Previous suggestions of the presence of nociceptive receptors in these non cartilaginous joint structures, which were made on a histological basis, had been thus confirmed by immunohistochemical methods.

The results of the present study were similar to Gartner and Hiatt(1994 who described Pacinian corpuscle ,located in the dermis and hypodermis, and mebtioned that they were mechanoreceptors composed of a core with an inner and outer regions, and a capsule which surrounded the core. The inner core invested the afferent nerve fiber which lost its myelin sheath soon after entering the corpuscle. The core cells were modified Schwan cells, while the component of the corpuscle were continuous, with the endoneurium of the afferent nerve fiber

The results of the present study were in agreement with Snell (2010) and Splittgerber (2019) who mentioned that The Pacinian corpuscle was rapidly adapting mechanoreceptor that was particularly sensitive to vibration. It could respond to up to 600 stimuli per second.Pacinian corpuscles were widely distributed throughout the body and were abundant in/68 the dermis. subcutaneous tissue , ligaments ,joint capsules ,pleura , periosteum,nippeles and external genitalia .Each corpuscle was ovoid in shape ,measuring about 2mm long and about 100 10 500 um across, It consisted of capsule and a central core containing the nerve ending , The capsule consisted of numerous concentric lamellae of flattened cells .A large myelinated nerve fiber entered the corpuscle and lost its myelin sheath and then its Schwann cell covering .The naked axon, surrounded by lamellae formed of flattened cells ,passed through the center of the core and terminated in an expanded end .

Golgi tendon organs

In the present study histological examination by light microscope of serial sections stained by Gordon and Sweet –silver impregnation of parts of TS of parts of anterior cruciate ligament ACL of full term:(33-36 weeks) (CRL 31-34cm) , synovial membrane SM and medial meniscus MM of the full term of the prenatal developing human knee joint, showed the presence of Golgi like tendon organs tha had periaxial space and large components in a capsule . The result of the present work were similar to Freeman and Wyke, who classified Golgi tendon organ as (type III) encapsulated mechanoreceptor in the cat joints–

The results of the present work were similar to Splittgerber (2019) mentioned that spindles (Golgi tendon organ)were present in tendons and were located near the junction of tendon with muscles. They provided the CNS with sensory information regarding the tension of muscles. Each spindle consisted of a fibrous capsule the sounded the a small bundles of loosely arranged tendon (collagen) fibers.(intrafusal fibers). The tendon.cells were larger and more numerous than those found else wherein the tendon.One or more myelinated sensory nerve fibers pierced the capsule ,lost their myelin sheath,branched and terminated in club-shaped endings.The nerve endings were activated by queezed by the adjacent tendon fibers within the spindle ,when tensspindleion developed in the tendon,Unlike the neuromuscular spindle ,which was sensitive to chages in muscle length,the neurotenenious organ detected the changes in muscle tension ,

The result of the present work were similar to Ovalle and Dow (1983) who compared the ultrastructure of the muscle spindle and the tendon organ of mouse and mentioned that the neruo tendenous and neurospindle consisted of outer capsule, periaxial space surrounded the selender inner capsules. ,whose component cells formed attenuated branches subdividing the axial space into several components for the nuclear chain and nuclear bag intrafusal fibes and their corresponding sensory terminals.

El Rakawy (1971) pointed that tendon spindle of Golgi consisted of nerve fibers which branched in special pattern on certain "thin" collagenous fibers which lied between the" thick" white fibers of the tendon. The thin (fine), collagenous fibers were surrounded with C.T.capsule. Meanwhile, Pacinian corpuscle was present in the C.T. in many places in human body. It was present in the deeper layers of subcutaneous tissue under the skin, in the C.T. near the tendons and joints, under the mucous membrane, in the mesentery as well as other places. It was large in size (3X2mms), and could be seen by naked eye. It looked like an onion as it was formed of a very thick C.T. capsule consisting of many concentric lamellae. A nerve fiber was found in the center of the capsule. Because they lied near the tendons and joints, they were thought to receive proprioceptive impulses and because they lied deep in the subcutaneous tissue they were thought to receive deep pressure.

The result of the present work was similar to Wu etal. (2015) found in the adult human ankle collateral ligaments that the Golgi tendon organs (type III) were thinly myelinated spindle-shaped corpuscles. It had the largest volume among the four types of the neouroreceptors they found in their study, with the mean size of 300 × 70 μm. The Golgi tendon organs were dyed bluish violet, with darker dyed shapelessly nerve substances. They existed singly or connected by nerve fibers. Although the Golgi tendon organs were found in all the ligaments, in their study, they were found less than Ruffini, which was not concordant with thr literature,

Free sensory nerve endings FNE in the prenatal developing ACL, SM and MM of human knee joint:

In the the present work ,histological examination of serial sections of TSof parts of ACL.SM and MM.of full trrm fetus showed the presence of Free sensory nerve endings FNE in the prenatal developing human knee joint .The results of the present work were similar to Wu et al. (2015) who studied and analyzed the pattern and types of sensory nerve endings in ankle collateral ligaments using histological techniques, in order to observe the morphology and distribution of mechanoreceptors in the collateral ligaments of cadaver ankle joint, and to provide the morphological evidence for the role of the ligament in joint sensory function.

The results of the present study agreed with El Rakawy (1971) who mentioned that in case of encapsulated nerve endings: the neurlemma of the nerve joined the capsule of the nerve and the naked nerve fiber usually ran a wavy tortuous course inside the capsule .The myelin ended where the nerve entered the capsule. He added that touch receptors from the surface of the skin downwards were Merkels corpuscle, Meissner Corpuscle and Plexus of Bounet.

The results of the present study agreed with Zimny (1986) who studied mechanoreceptors in the human anterior cruciate ligament and reported that In addition to free nerve endings, two morphologically distinct mechanoreceptors were identified: (1) Ruffini end organs and (2) Pacinian corpuscles.

The results of the present study were similar to the results of Munger and Ide (1987) who mentioned that Meissner corpuscles were a typical corpuscular receptor of murine (Ide, 1976, 1977), marsupial and primate glabrous skin. The axons typically weaved back and forth between stacks of lamellae. They mentioned that Hair follicles of most species studied to date (the exception being the rabbit and to some extent the guinea pig) were multiply innervated with lanceolate, Ruffini and free nerve endings FNEs. The lanceolate terminals were the rapidly adapting terminals that were numerous in guard hairs. Ruffini terminals of hairs resembled those of the periodontal ligament or joint capsules and both were remarkably similar to Golgi tendon organs in terms of ultrastructural characteristics. The key ultrastructural characteristic was the encircling of collagen bundles by axons and associated Schwann and connective tissue cells. Axons frequently entered the epidermis either to terminate as FNEs or became associated with Merkel cells in glabrous skin at the base of the papillary ridges or in clusters of Merkel cells in hairy skin in touch domes. Merkel cells had clusters of apparent secretory granules polarized toward the axon and the axon was typically a slowly adapting mechanoreceptor. The function of the granules was not known. Pacinian corpuscles were the largest of the corpuscular receptors of the dermis and were characterized by an elaborate inner core of stacks of numerous thin lamellae arranged in a bilaterally symmetrical manner. They mentioned that based on the fact that the lamellae were coupled with gap junctions and the outer core lamellae isolated by numerous tight junctions, the authors had proposed that the unique ionic environment might be in part responsible for the remarkable sensitivity of Pacinian corpuscles

The results of the present work coincided with Krebs, Weiberg, Akesson (2012) who mentioned that Meissner corpuscles were encapsulated receptors composed of a stack of epithelial cells with axon winding throughout that stack . They were rapidly adapting and sensitive to light touch. Merkel endings and Meissner corpuscles were receptors responsible for fine touch and fine discrimination in finger prints.The Pacinian corpuscles were encapsulated receptors deeper in the skin in the hypodermis, below the dermis were composed of concentric layers of epithelial cells. They were rapidly adapting and therefore could respond to quickly changing stimuli. Pacinian corpuscles detected vibration.

Snell (2010) and Splittgerber (2019) classification of the neuroreceptors (Table 2) were similar to the classification of Freeman and Wyke.However Standrig et al. (2016), differed in illustrating the function of the receptors in articulating joints (Table3).

The results of the present study were similar to Mine et al. (2000) who studied using histology, the innervation of nociceptors in the medial and lateral menisci of the knee joint. Specimens examined were taken from 16 patients during arthroplasty. The patients were 6 men and 10 women, with ages ranging from 14 to 76 years (mean 56 years). Immunohistochemistry with the unlabeled antibody biotin-streptavidin method was employed to detect protein gene product 9.5 (PGP 9.5) or substance P (SP) in the specimen. The antibody for PGP 9.5 detected nerve tissues in the menisci. Most but not all of the nerve fibers were associated with blood vessels. Nerve fibers and sensory receptors were found mainly in the peripheral, vascular zone, representing the outer one-third of the meniscus, and the innervated area was wider in the anterior and posterior horns. Pacinian and Ruffini corpuscles as well as free nerve endings were identified in these areas. Larger fibers coursed circumferentially in the peripheral zone, with smaller branches of nerve fibers running radially into the meniscus. Nerve fibers positive for SP were also detected in the menisci, but were fewer in number. Their branches also were fewer, oriented radially and paralleling blood vessels. They mentioned that their study showed that some of the pain in cases of meniscal tear could originate in the meniscus itself, especially with peripheral tears that might be accompanied by bleeding.

The results of the present study agreed with Lin et al. (2019) who mentioned that the mechanism of pain after meniscus injury remained unknown. After injury, some individuals suffered from acute pain, while others suffered from delayed pain. A precise nociceptor distribution pattern might provide the answer to that question. They studied twenty-two intact menisci (paired medial and lateral menisci) obtained from 11 patients with a mean age of 28.45 years. All menisci were sectioned into five parts: the anterior horn, anterior body, middle body, posterior body, and posterior horn. Two paired menisci were stained by a modified gold chloride method. All other specimens were stained by H&E staining and were subjected to immunohistochemical staining to detect substance-P (SP). Under a microscope, measurements were made in 10 consecutive visual areas at 400x magnification. SP-positive fibres were determined using a three-grade scale, and the mean number of SP-positive fibres was assessed. They noted that nerve fibres and nociceptors stained by H&E and modified gold chloride were found mainly in the vascular outer third of the menisci as observed under a microscope; the positive area was wider in the anterior and posterior horns. There were more SP+ fibres in the anterior horn and posterior horn than in the anterior body, middle body, or posterior body ($p < 0.05$). Regarding the bodies, the mean number of substance-P fibres was greater in the anterior body or posterior body than in the middle area ($p < 0.05$). No significant differences were found between the number of substance-P nerve fibres in the anterior horn vs the posterior horn or in the anterior body vs the posterior body of all menisci ($p > 0.05$). No significant differences were observed in the same location between the paired medial and lateral menisci in all areas of the menisci ($p > 0.05$). They conclude that the density of nociceptors decreased along the longitudinal axis of the meniscus from both horns to the middle part of the body, which might guide future diagnostic methods and rehabilitation protocols

The results of the present work agreed with Standring et al. (2016) who mentioned that meylinated axon in articular nerves innervated Raffini endings, lamellated articular corpuscles responded to rapid movement and vibration, and adapt rapidly both types of receptors registered the speed and direction of movement. Golgi tendon organs innervated by the largest mylinated axon (10-15u m diametr),were slow to adapt ,they mediated position sense and also were concerned in stereognosis .i.e.recognition of shape of held objects .Simple endings were numerous at the attachment of the capsule and ligaments ,and were thought to be terminals of unmylinated and thinly mylinated nociceptive axon. The unmylinated post ganglionic sympathetic axons terminated near vascular smooth muscle ,and were presumably either vasomotor or vasosensory .The endings in synovial membrane were believed to supply blood vessels exclusively, from which it was assumed that synovial membrane was normally relatively insensitive to pain.

The results of the present work agreed with Johansson et al. (1991) who mentioned that the adult knee joint ligaments contained Ruffini, Pacinian, Golgi, and free-nerve endings with different capabilities of providing the CNS with information about movement and position as well as about noxious events. Skeletomotor neurons (alpha-motoneurons) were known to be influenced only very rarely and weakly from low-threshold mechanoreceptors in the ligaments, while the effects on the tau-muscle-spindle system in the muscles around the knee were so potent that even ligament stretches at very low loads might induce major changes in the responses of the muscle spindle afferents. Since the primary muscle spindle afferents participated in the regulation of muscular stiffness, the receptors in the knee joint ligaments probably contributed, via the tau-muscle-spindle system, to preparatory adjustment (pre-setting) of the stiffness of the muscles around the knee joint, and thereby to the joint stiffness and the functional joint stability.

The results of the present work coincided with Turlough Fitzgerald et al. (2012)reported that Ruffini endings were found in both hairy and glabrous skin responded to drag (shearing stress)and were slowly adapting. Their structure resembled that of Golgi tendon organ having collagenous core in which several axons branched liberally .Pacinian corpuscles were the size of rice grain. They numbered about 300 in the hand. They were subcutaneous ,close to the underlying periosteum numerous along the sides of the fingers and in the palm.Inside a thin connective sheath were onion like layers of perineural epithelium containing some blood capillaries .Inner most were several teloglial lamellae surrounding a single central axon that had shed its myelin sheath at point of entry. Pacinian corpuscles were rapidly adapting, and were especially responsive in vibration –particularly to bone vibration in the limbs ,many corpuscles were embedded in the periosteum.of long bones.Pacinian corpuscles discharged one or two impulses when compressed, and again when released .In the hands ,they seemed to function in group mode :when an object such as orange was picked up ,as many as 120 or more corpuscles were activated momentarily, with a momentarily repetition when the object was released .For that reason, they had been called "event detectors " during object manipulation.

In the present study parts of menisci of 4 month fetus (13-16wks-CRL 9-14cm) and full term (33-36 weeks) (CRL 31-34cm) showed the presence of free nerve endings. Free nerve endings increased with age progress. Meissner corpuscles had striated appearance were seen in the parenchyma of medial meniscus in full term :(33-36 weeks) CRL 31-34cm). Meissner corpuscles were ovoid in shape and consisted of a stack of modified flattened Schwann cells arranged transversely across the long axis of the corpuscle. The corpuscle was enclosed by a capsule of connective tissue that was continuous with the endoneurium of the nerves that entered it. Some authors attributed pain sensation to Meissner corpuscles (Meghan et al., 2021)

Meghan et al. (2022) reported that differences in corpuscular density had been associated with a number of neurologic disorders, including sensory neuropathy, Charcot-Marie-Tooth disease, Parkinson's disease, HIV neuropathy, and Friedreich's ataxia. Nolano et al. (2008) Almodovar et al. (2011); Almodovar (2012) Hypertrophy and hyperplasia of Meissner corpuscles had been described during the initial stages of diabetes in primate studies. Fellegara et al. (2008). Following chronic hyperglycemia, hypertrophy of the corpuscles decreased; although the number of corpuscles remained greater than those of non-diabetic control animals, the receptors continued to display abnormal structure and protein expression. Additionally, the reduction of neuronal axons in the dermis, including those innervating Meissner's corpuscles, had been observed in patients with diabetes. Shun et al. (2004). Axonal degeneration to Meissner's corpuscles and the dermis thus suggested the peripheral neuropathy experienced by people with diabetes.

Meissner corpuscles could survive for long-periods following nerve injury or denervation but could sustain alterations in protein expression. Expression of S100, a marker of lamellar cells within Meissner corpuscles, had been shown to be normal following spinal cord injury, diminished in nerve entrapment, and absent in denervated dermatomes. Albuerne et al. (1998). Those findings suggested that the functional integrity of axonal innervation was required for S100 protein expression by corpuscular lamellar cells. Márquez et al. (1997).

The results of the present study agreed with Krauspe et al. (1995) who described the distribution of neurofilament containing nerve fibers and corpuscular like endings in the human anterior cruciate ligament using immunocytochemical study. They found neurofilament –positive fibers in the bundles. The bundles were mostly located near blood vessels in the subsynovial layer and in interfascicular gaps. Only a few single nerve fibers were found independent of blood vessels.in inter fascicular gaps.a and between collagen bundles. Two types of corpuscular -like endings were found i.e. "spiral like "type I and spray like"type II endings .Similarly to nerve fibers, both types of corpuscular -like endings were found mainly near the tibial and femoral attachment sites. They added that most likely "type I and "type II corpuscular -like endings served a mechanoreceptive function involved in the sensory control of normal movements and stress function.

In the present study histological examination by light microscope of serial sections stained by Gordon and Sweet –silver impregnation of parts of anterior cruciate ligament of full term:(33-36 weeks) (CRL 31-34cm) , medial meniscus MM and synovial membrane SM of the full term of the prenatal developing knee joint, showed the

The results of the present study were similar to Wu, et al. (2015) who studied the morphology of mechanoreceptors in collateral ligaments of the adult human ankle joint and mentioned that the Ruffini formed dendritic nerve endings ended at thinly myelinated spindle corpuscle. They were dyed bluish violet, forming a cluster of two to five corpuscles with 60×25 μm, which were found in all ligament samples. Meanwhile; Wu et al. (2015) mentiond that the Pacini were a thickly myelinated coniform or broom-shaped corpuscles. Pacini was also found in single or as botryoidal cluster formed by more than ten corpuscles connected by axonal fibers with the size of 150×40 μm. The dark purple-dyed cylindrical structure was the axonal fibers stretched into the Pacini, with the diameter of 5–10 μm. As more than ten concentric circles of darkly dyed flat cells were surrounded by an axonal fiber, the Pacini had another name of lamellar corpuscle. The morphological structure of an axonal fiber surrounded lamellar layers appeared to be diverse. Wu, et al. (2015) added that Concordant to other reports, direction of Pacini axon had the same direction parallel to the direction of collateral ligaments. A large number of Pacini existed in the synovial tissues and the ligament at both ends of the collateral ligaments, which were accompanied by the nerve vessel bundles. Basically, the Pacini in the synovial and ligament tissue intervals were in smaller size than those in the ligament parenchyma. They found that the Pacinian corpuscles were the most common mechanoreceptors in all the ankle collateral ligaments.

In the present work, histological examination of serial sections 0f parts of the developing medial meniscus of 4 month fetus(13-16wks-CRL 9-14cm) and full term human:(33-36 weeks) (CRL 31-34cm) ,the anterior cruciate ligament and the synovial membrane of full term,showed the presence of free nerve endings(FNE) around blood vessels . (FNE) might respond to pain and stretch of these knee structures.

The results of the present work were in accordance to Standring et al. (2016) who mentioned that cartilaginous structures within joints normally had no nerve supply partly because they were avascular and partly because axonal growth was inhibited by a high concentration of proteoglycan. However, when fibrocartilage was injured or diseased, nerves might accompany the consequent ingrowth of blood vessels and gave rise to pain (Freemont et al.,1997) Subchondral bone was normally innervated and was a likely source of pain in the spine the capsule.

The results of the present work agreed with Belluzz et al., 2019 who mentioned that, since sensory nerve fibers were involved in pain perception and in the secretion of proinflammatory SP, while sympathetic nerve fibers secreted anti-inflammatory catecholamine (in particular norepinephrine and endogenous opioids) inhibiting pain perception, it was likely that a cross-talk with sensory fibers might exist.

In the present study histological examination by light microscope of serial sections stained by Gordon and Sweet –silver impregnation of parts of anterior cruciate ligament of full term showed the presence of spray nerve endings and structures similar to flower .That agreed with Snell 2010 mentioned that the flower -spray endings were situated mainly on the nuclear chain fiber some distance away from the equatorial region. A mylenated nerve fiber slightly smaller than that for the annulospiral ending pierced the capsule and lost its myelin sheath and the naked axon branched terminally and ended as varicosities, it resembled a spray of flowers. Stretching(elongation) of the intrafusal fibers resulted in stimulation of the annulospiral and flower-spray endings, and nerve impulses passed to the spinal cord in the afferent neurons .Motor innervation of the intramural fibers was provided by fine gamma motor fibers. The nerve terminated in small motor end plate stimulated at both ends of the intrafusal fibers. Stimulation of the motor nerves caused both ends of the intrafusal fibers to contract and activated the sensory endings .The encapsulated region, which was without cross striations ,was non-contractile. The extrafusal fibers of the remainder of the muscle received their innervation in the usual way from large alpha size axon.

The results of the present work were similar to Belluzzi et al. (2019) mentioned that many Catecholamines,Growth Factors were secreted by the synovial membrane Among growth factors, NGF, VEFG, and TGF-β, Belluzzi et al. (2919) mentioned that NGF was a soluble neuropeptide belonging to neurotrophin family; it was involved in the development of the nervous system (i.e., growth, maintenance proliferation and survival of neurons) but also in pain processing which could be caused by direct and indirect mechanisms . Direct mechanisms involved activation of its high-affinity receptor (i.e., NGF tyrosine kinase receptor TrkA) located at the surface of sensory neurons and by the low-affinity for receptor p75 , followed by activation of different signaling pathways leading to the nociceptive pain. In parallel, another receptor that seemed to mediate development of NGF-induced hyperalgesia was the transient receptor potential channel vanilloid 1 (TRPV1); in fact, the block of TRPV1 attenuated, as demonstrated by Mills et al., thermal and mechanical NGF-induced hyperalgesia in rats . Interestingly, it functions to modulate

In the present study histological examination of sersail section of parts of TS of the anterior cruciate ligamentACL , medial meniscuMMs,and synovial membrabeSM of the prenatal full term of human developing knee joint, showed the presence of Pacinian corpuscles that were large and found single in the anterior cruciate ligament ,and were small more than one around blood vessels in the synovial membrane, Pacini corpuscles were not noted in the medial meniscus . Golgi l[ke tendon organ was seen capsulated in single form in the synovial membrane ..Free nerve endings were found around the blood vessels in the synovial membrane, medial meniscus and tissues of anterior cruciate ligament .They were least in the medial meniscus. Ruffini formed dendritic nerve endings and ended at thinly myelinated spindle corpuscle or some times ramification with button ends. They were smaller and more frequent in the synovial membrane than those seen in the medial meniscu of rge developing prenatal human knee joint. Messiener corpuscle had zigzag,or spira lnerve endings giving striated appearance of the corpuscle .They were seen in the anterior cruciate ligament, synovial membrane and medial meniscus.The presence of Pacini corpuscles in the synovial membrane in more than one might be to accommodate for the rapid function in group mode activated momentarily response.

Flower end neuronal structures and expanded varicosities in ACL of the prenatal developing human knee joint

In the present work histological examination of parts of serial sections stained by Gordon and Sweet –silver impregnation method of parts of ACL of the knee joint of full term fetus showed, the presence of neuronal ends resembled flower spray .and end expanded varicosities structures .There were bundles of nerves seen in Single row or chain, they extended beyond the capsule at each end.

The results of the present work were similar to who Splittgerber R 2019 mentioned that the neuromuscular spindle .or muscular spindle were found in skeletal muscle and were most numerous towards the tendenous attachment of the muscle.T hey provided the CNS with sensory information regarding the muscle length and the rate of change in the muscle length. The CNS used that information to control muscle activity. Each spindle measured about 1-4mm in length and was surrounded by a fusiform capsule of CT .Within the capsule were 6-14 slender muscle spindle fibers the ordinary muscle fiber situated out side the spindle were referred to as extrafusal fibers. The intrafusal fibers of the spindle were of two types: the nuclear bag and the nuclear chain fibers. The nuclear bag fibers were recognized by the presence of numerous nuclei in the equatorial region, which consequently expanded, also cross striations were absent in that region. In the nuclear chain fibers, the nuclei formed a single row or chain in the center of each fiber at the equatorial region. The nuclear bag fibers were larger in diameter than the nuclear chain fibers, and they extended beyond the capsule at each end to be attached to the endomysium of the extrafusal fibers. The two types of sensory innervation of muscle spindle were annulospiral and flower spray. The annulospiral were situated at the equator of the intrafusal fibers .As the large mylenated nerve fiber pierced the capsule,it lost its myelin sheath and the naked axon winided spiraly around the nuclear bag or chain portions of the intrafusal fibersThe flower spray were situated mainly on the nuclear chain fibers ,some distance away from the equatorial region.A mylenated nerve fiber slightly smaller than that for the annulospiral ending pierced the capsule, and it lost its myelin sheath and the naked axon branched terminally and ended as varicosities: it resembled a spray or flower. Stretching(elongation) of the intrafusal fibers,resulted in stimulation of the annulospiral and flower spray endings,and the nerve impulses passed to the spinal cord in the afferent neurons.

Motor innervation of the intrafusal fibers was provided by fine alpha motor fibers .The nerve terminals in the small motor end plate. Stimulated at both ends of the intra-fusal fibers. Stimulaton of the motor nerve s caused both ends of the intrafusal fibers to contract, and activate the sensory endings. The equator ial region, which lacked/ cross straition was contractile. The Extrafusal fibers, oF the remainder of the muscle received the innervation from large alpha sized axon.

Conclusion

In the present study, the presence of diferent, many neuronal receptors and nerve ending in the intra articular small knee structures studied; ACL, SM, MM, seen by light microscope , indicated sensory functions o these neuroreceptors essential for knee kinesiology and biomechanics . The crowding of various tiny complicated ,numerous, neuro receptors and free nerve endings , in minute , knee structures indicated the presence of the most only powerful Creator , the most merciful the most Graceful Allah .Suret Al Ensan 28, Suret Al thareate 21 .Suret Fusilate 53, Suret Lokman 11. Suret Fater 40,Allah sword om the truth of the Prophet of Islam by the stuctures that were not seen as those minute neuroreceptors in the prenatal developing human knee joint,as they were seen only under microscope :suret el haka 39

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NB: WORTH MENTION: TO WHOM IT MAY CONCERN:

ALL THE PAPERS published by Nasra Ayoub, ABOUT MUSK AND BASIL(OCIMUM BASILCUM) WERE STOLEN FROM Prof MANAL G ABD ELWAHAB,THE PAPERS WERE stolen, by Nasra Ayoub,Soad Hanem, Fergani,Mansi ,Alaa El Deen ,as the work about aromatherapy by musk and basil were published in the magazines of Ejaz, Muslim world League THE year 1433 HIJI number 40 pp 11&41pp34 and on the cover of the magazine In addition,Prof Manal . produced and discussed five written projects in English about MUSK AND BASIL aromatherapy in front of the scientific committee of the chair of applied Prophetic Medicine at King Fahd center, KING Abdul-Aziz university-Jedda -KSA, in the presence of ,Prof MOSSA Shaker.Soad jaoni, ,Prof Sawsan Rohayem THE Prof of the chair ,and 40 international scientists and the signature of the attendance ,besides the secretory of the chair Rasha.Nasra Ayoub stole one single research about musk -THE FIRST SERIAL PAPERS OF MUSK and Badi from one experiment .Nasra Ayoub stole more than 10 shared papers ,and attributed the work to her self first name.,Soad Stole more than7 papers. The work of musk and basil was after dedicating reaches for 10 years by Prof Manal. Nasra atrebuted only one paper about musk to Manal and another 4 shared papers only as she was responsible for pulishing.Prof Manal provided Nasra Ayoub and Soad shaker by written Ehglsh information and how mechanism the musk and Basil worked .intoduction and discussion ,they know nothing about . Nasra Ayoub And Soad SHAKED stole the intellectual property of Prof DrManal and desieved and WERE NOT HONEST published without Manal knowledgment.Nasra and Soad attributed two papers to themselves and 4 other thieves, whom had nothing to do with the project ,although the project and the the applied experiment was one belonged to Manal .Nasra cheated and signed the name of Manal on the contract of King Abd Aziz university with out the knowledge of Prof Manal. Soad Jaoni,Abd Gawad SAWI,and shiek Abullah

MUSLEH took the thieves NASRA and Soad SHAKER TO PRESENT THE STOLEN PAPERS ,TO Dubie conference, the year 2019. Soad Jaon, the survisor of the chair of the prophetic medicine ,Abd GAWAD SAWI, shiek MUSLEH had kwon that the papers were stolen ,in spite of that, they took the thieves and supported them to present the stolen papers.Only the good HONEST straight person was Prof dr KORAYEM who was the director of the research unit in the university and chief editor of Ejaz magazine had terminated the presence of Nasra and Soad Shaker from the research unit in the university after their not-honest work and steeling of the work of Prof Dr , Manal about musk and basil.

We REGRET THAT Prof Dr Manal added Nasra Ayoub And Soad to 4papers about muskand basil published in Zakazik conference- Azhar university the year 2016 SHAKEDmas Manal did not know their un honest work and steeling her papers and attributed that to themselves.

We Manal G Abd El Wahab are very sorry to announce that,

a We refuse the un honest deeds of the thieves Nasea Ayoub,Soad ShaKER,AND who supportrd them and allowed their participation in Dubei conerence with the stolen 8 papers about musk and basil,which are intellectual property of Manal G Aba El.We will ان شاء الله use legal writes.

Author contribution"

• Role of Manal G. Abdelwahab- :Knee Dissection, collecting specimens ,staining slides, photographing , writing and revising the paper.

• Role of-Sohair A. Sadek: collecting the miscarriages.

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