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Bone, Certain Disorders and Diagnostic Tests: An Overview

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ABSTRACT

Background: The term bone, with extremely complex structures, refers to a type of substances that have evolved to accomplish a variety of mechanical functions. Along with the numerous functions of bones, they may suffer from some problems such as cancerous and non-cancerous disorders. **Results:** In the present study, a brief overview of the different types of bone cells, the functions, bone development mechanism, growth factors, some certain bone disorders, diagnostic tests and clinical treatments are highlighted. **Conclusion:** All in all, the information reviewed in this study provided insight into the bone, the cells, the functios, some disorders and methods of their treatments.

Key words: Bone, bone cells, osteosarcoma, tumors, treatments

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INTRODUCTION

Bone is one of several types of connective tissue found in the body that generally implies tissue with an extracellular matrix high in collagen and found surrounding other, more specialized organs. Other examples of connective tissue include cartilage, ligament, tendon, muscle and even blood. Bone serves three functions in the human body; it provides mechanical support and muscle attachment, it provides a protective shield for internal organs and marrow and it provides stores of ions necessary for normal bodily function[1]. Bones support and protect the different organs of the body, producered and white blood cells and store minerals. Bones have a variety of shapes. Moreover, they have a complex internal and external structure. A typical bone constitutes several types of cells: Osteoblasts, bone lining cells, osteocytes and osteoclasts. Bones main functions include: Protection, structure, movement and sound transduction.

Due to the numerous and complex functions of bones, there are various types of bone disorders that require clinical treatments. These conditions consist of cancerous disorders and non-cancerous (benign) disorders[2]. The aim of this study is to give an overview regarding the different types of bone cells, their functions, bone development mechanism, growth factors, bone disorders, the diagnosis and treatments.

BONE BIOLOGY

Bone is a rigid organ that constitutes part of the endoskeleton of all vertebrates. Bones generally have two types (1) Cortical bone (compact bone) and (2) Trabecular bone (cancellous or spongy bone). Bone is composed of several different cell types each with their own specific function and an extracellular matrix. The matrix is composed of 95% type I collagen and 5% proteoglycans and noncollagenous proteins. Proteoglycans are high molecular weight complexes of proteins and polysaccharides typically found in structural and connective tissues. One example of a proteoglycan is a glycosaminoglycan, commonly found in both bone and cartilage. Partially what makes bone a unique tissue type is its ability to form and deposit crystalline salts. These salts form a mineralized coating around cells in its extracellular matrix, providing strength and rigidity, however, the bone still has some inherent flexibility. The mineralized coating is composed primarily of calcium and phosphate in a ratio that forms hydroxyapatite. It is this matrix that also provides the body with necessary ions such as calcium and phosphate[3].

Cells in bone tissue: The bone cells include four different types: Osteoblasts, osteocytes, bone lining cells and osteoclasts. Osteoblasts are fully differentiated cells that originate from either bone marrow stromal cells or mesenchymal stem cells, proliferate and differentiate to pre-osteoblasts and then to mature osteoblasts. Once differentiated, osteoblasts secrete both type I collagen and the noncollagenous proteins necessary to produce the mineralized bone matrix. Osteoblasts are usually found lining areas of newly formed and unmineralized tissue, usually comprised of type I collagen (osteoid tissue). In the synthesis of mineralized tissue, osteoblasts line up along the osteoid tissue, secrete the necessary components of mineralization and eventually become surrounded by the

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mineralized extracellular matrix. The osteoblast at this point has become fully mature and is considered an osteocyte[4].

Mechanism of bone development: Bone development can be described by two distinct mechanisms, involving two distinct bone types. Intramembranous ossification describes the formation of flat bones (skull bones, scapulae, mandible, pelvic bones) while endochondral ossification describes the formation of long bones (femur, tibia, fibula, humerus, radius, ulna)[5].

Stem cell to osteoblast: A comprehensive discussion of the osteoblast and its lineage must begin with the stem cell. Stem cells are generally divided into three categories; embryonic stem cells, hematopoietic stem cells and mesenchymal stem cells[6]. Hematopoietic and mesenchymal stem cells are principally found in bone marrow, which specifically contains hematopoietic precursors, differentiated hematopoietic cells, a connective tissue network called stroma (which is a heterogeneous mixture of cells including adipocytes, reticulocytes, endothelial cells) and fibroblastic cells which are in direct contact with the hematopoietic elements. Stroma contains cells which differentiate into bone, cartilage, fat and a connective tissue which supports the differentiation of hematopoietic stem cells[7].

There are criteria set aside for the classification of stem cells. According to Canalis[8] stem cells are classified as such based on their function as compared to other cell types. A stem cell of a particular tissue type would be a cell:

- Lacking certain tissue-specific differentiation markers
- Capable of proliferation
- Able to self-maintain the population of cells
- Able to produce many differentiated, functional daughter cells
- Able to regenerate the appropriate tissue after injury

Growth factors and morphogenetic proteins: The growth factors and other proteins that exist in bone are responsible for regulating cellular activity. Growth factors bind to receptors on cell surfaces, stimulating the intracellular environment to act. Generally, this activity translates to a protein kinase that induces a series of events that result in the transcription of mRNA and ultimately into the formation of a protein to be used intra- or extra-cellularly. The combination and simultaneous activity of many factors results in the controlled production and resorption of bone. These factors, residing in the extracellular matrix of bone, include transforming growth factor-ß (TGF-ß), insulin-like growth factor (I and II) (IGF), Platelet Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF) and the Bone Morphogenetic Proteins (BMPs)[9]. Researchers have been able to isolate and in some cases synthesize, these factors and thus examine the particular function of each factor to improve normal bone development. The ability to isolate appropriate factors from bone, synthesize them in large quantities and reapply them in concentrated amounts to speed up bone healing has produced numerous possibilities for bone graft substitutes[4].

Transforming growth factor: The factor is known as TGF-ß. TGF-ß is a generic name that refers to three structurally and functionally related growth factors TGF-ß1, -ß2 and ß3, all of which are found in mammals[10,11]. Through knock-out studies in mice, it has been found that a lack of TGF-ß1 may have an effect on the developing immune system and therefore may be involved in hematopoiesis. Related reports have included several functions under the direct or indirect control of TGF-ß such as skin formation, inflammatory fibrotic disease, tumor development, angiogenesis, hematopoiesis, mammary gland development, wound healing and bone metabolism[11].

Platelet-derived growth factor: Platelet-derived growth factor exists as three similar molecules, PDGF-AA, -BB and -AB, with molecular shape and locus of activity distinguishing them from one another (-BB and -AB act systemically while -AA acts locally). PDGF is synthesized by platelets, endothelial cells and macrophages and stimulates the proliferation of osteoblasts and other cells derived from mesenchymal stem cells. In addition, increases collagen and non-collagenous protein production. Although its role is not fully clear, elevated levels have been noted during fracture healing[12].

NORMAL BONES

Bones may be known as just being part of the skeleton, like the steel girders that support a building, however, bones actually have a number of different functions. Some bones support and protect the vital organs. Those are: The skull bones, breast bone (sternum) and ribs. These types of bones are called flat bones. Other bones, such as those in the arms and legs, make a framework for the muscles that assist to move[13].

Furthermore, bones make new blood cells. This is conducted in the soft, inner part of some bones called the bone marrow, which contains blood-forming cells. New red blood cells, white blood cells and platelets are made in bone marrow. Moreover, bones provide the body a place to store minerals such as calcium. Because bones

are very hard and do not change shape once man reaches adulthood, it may be thought as being dead, while they are complex living tissues. Like all other tissues of the body, bones have many kinds of living cells. Two main types of cells in the bones help them stay strong and keep their shape:

- Osteoblasts assist build up bones by forming the bone matrix (the connective tissue and minerals that give bone its strength)
- Osteoclasts prevent too much bone matrix from building up and help bones keep their proper shape. By depositing or removing minerals from the bones, osteoclasts control the amount of these minerals in the blood as well[4]

BONE MALIGNANCY

The body has many living cells. Normal cells grow, divide and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer but they all start because of out-of-control growth of abnormal cells[14]. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells are able to invade other tissues, something that normal cells can not do. Cells become cancer cells due to damage to DNA. DNA is in every cell and controls all the actions. In a normal cell, when DNA damages the cell repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, however the cells do not die like they should. As an alternative, these cells go on making new cells that the body does not require. These new cells will all have the same damaged DNA as the first cell does[15]. Damaged DNA can be inherited, however most DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in the environment. Sometimes the cause of the DNA damage is something clear, such as cigarette smoking however often no obvious reason is found.

Osteosarcoma: Osteosarcoma, a most common bone cancer, is an malignant neoplasm that arises from primitive transformed cells of mesenchymal origin. It produces malignant osteoid. This cancer is the eighth most common type of childhood cancer. It is slightly more common in males than in females[16].

Factors affecting osteosarcoma: A risk factor is a factor that affects the opportunity of getting a disease like cancer. Lifestyle-related risk factors are significant in numerous cancers in adults. Examples of lifestyle-related risks consist of obesity, unhealthy diets, not getting enough exercise, smoking and drinking too much alcohol. However, dissimilar to a lot of adult cancers, lifestyle-related risk factors do not seem to play a big role in childhood cancers, such as osteosarcomas[14].

Age and height: The possibility of osteosarcoma is highest during the teenage "growth spurt." Youth with osteosarcoma usually are tall for their age. This indicates there may be a connection between rapid bone growth and risk of tumor formation[14].

Gender: Osteosarcoma is more common in males compared with females. Females tend to develop it at a somewhat earlier age, probably because they tend to have the growth spurts earlier[14].

Race/ethnicity: The possibility of osteosarcoma is slightly more common in African Americans compared to whites. Radiation to bones, people who were treated with radiation therapy for another cancer may increase risk of later developing osteosarcoma. Being treated at a younger age and with higher doses of radiation (doses of more than 60 gray or Gy), both raise the danger of developing osteosarcoma. X-rays or other imaging tests that check the inside of the body do not seem to elevate the danger of developing osteosarcoma[14].

What causes osteosarcoma: Scientists have found that osteosarcoma is linked with a number of other conditions, which were described in the previous section on risk factors. But most patients with osteosarcoma do not have any known risk factors[5]. Over the past few years, scientists have made great progress in understanding how certain changes in DNA can cause cells to become cancerous. A copy of the DNA is in each cell of the body. It carries the instructions for almost everything the cells do. People usually look like the parents because they are the source of the DNA. However, DNA affects more than how people look. It influences the risks for developing certain diseases, including some kinds of cancer[11].

Some genes (parts of the DNA) include instructions to control when the cells grow and divide. Genes that encourage cell division and cause cells to live longer are known as oncogenes. Others that slow down cell division or cause cells to die at the right time are called tumor suppressor genes[5]. Cancers can be caused by DNA mutations (changes) that turn on oncogenes or turn off tumor suppressor genes.

Some people with cancer have DNA mutations they inherited from a parent; in this situation, all the cells in

the body carry the mutation. These are called germline mutations. These mutations increase their risk for the disease. Usually, however, cancer causing mutations are acquired during life rather than inherited before birth; in this case, the mutation occurs only in the cells that will develop the cancer. These are called somatic mutations.

CERTAIN BONE DISEASES

Paget disease of the bone: Paget disease, a chronic disorder that results in enlarged and misshapen bones, is a benign, however, pre-cancerous condition that affects one or more bones. It frequently affects people older than 50. This disorder causes abnormal bone tissue to form, affected bones are heavy and thick however are weaker than normal bones[10]. This situation is not life-threatening however bone sarcomas develops in about 1% of people who are suffering from Paget disease, usually when a lot of bones are affected.

Multiple hereditary osteochondromas, osteochondromas are benign bone tumors formed by bone and cartilage. Each osteochondroma has a very slight risk of developing into an osteosarcoma. Most osteochondromas are cured by surgery. However, some people inherit a tendency to develop many osteochondromas and it may not be possible to remove them all. The more osteochondromas a person has, the greater the risk of developing osteosarcoma[17].

Malignant (Cancerous) bone tumors: Ewing tumors are the second most common malignant bone tumor in children. Most other types of bone cancers are usually found in adults and are rare in children. These include chondro sarcoma (cancer that develops from cartilage), malignant fibrous histiocytoma, fibrosarcoma, chordoma and malignant giant cell tumor of bone.

Numerous types of cancer that begin in other organs of the body can spread to the bones. These are referred to as metastatic bone cancers, however they are not real bone cancers. For instance, prostate cancer that spreads to the bones is still considered as prostate cancer[18].

Benign (Non-cancerous) bone tumors: All bone tumors are not malignant. Cells that form benign tumors, a mass of cells that are not able to invade neighboring tissue or metastasize, can not spread to other parts of the body. They are not life threatening and can be removed by surgery. There are numerous types of benign bone tumors:

- Osteomas are benign tumors formed by bone cells
- Chondromas are benign tumors formed by cartilage cells
- Osteochondromas are benign tumors with both bone and cartilage cells

Other benign bone tumors include eosinophilic granuloma of bone, non-ossifying fibroma, enchondroma, xanthoma, giant cell tumor and lymphangioma[18].

DIAGNOSTIC TESTS

Imaging tests: Imaging tests employ X-rays, magnetic fields or radioactive substances to make images of the inside of the body. Imaging tests may be performed for some reasons such as:

- To assist find out if a suspicious area might be cancerous
- To learn how far cancer may have spread
- To assist determine if treatment has been efficient

Bone X-ray: Phisitions suspect or recognize osteosarcoma on regular X-rays of the bone. However other imaging tests may be needed as well. Even if results of an X-ray strongly suggest an osteosarcoma, a biopsy will still be needed to confirm that it is cancer rather than some other problem, such as an infection[19].

Magnetic resonance imaging (MRI) scans: MRI scan provides detailed images of soft tissues in the body however MRI scans employ radio waves and strong magnets rather than X-rays, therefore no radiation is involved. The radio waves' energy is absorbed by the body and afterward released in a pattern formed by the type of body tissue and by specific diseases. A computer translates the pattern into a clear photo of parts of the body. Frequently, an MRI scan is conducted to interprate a bone mass observed on an X-ray. MRI scans indicate if the mass is possibly to be a tumor, an infection or some type of bone damage from other reasons. In addition, MRI scans assist to determine the precise extent of a tumor, as they provide a detailed and clear view of the marrow inside bones and the soft tissues around the tumor. Occasionally, the MRI assist to discover small bone tumors several inches away from the main tumor which is known as skip metastases. Defining the amount of the tumor is very significant for surgery. An MRI scan generally shows better details than a CT scan[19].

Computed tomography (CT) scan: The CT scan is an X-ray test that produces detailed cross-sectional images of parts of the body. Instead of taking one picture, like a regular X-ray, a CT scanner takes many pictures as it rotates around a person lying on a table. After that, a computer combines the pictures into images of slices of the part of the body being investigated. Unlike a regular X-ray, a CT scan shows detailed images of the soft tissues in the body[20].

Biopsy: Even though the results of imaging tests suggest that cancer is present, a biopsy (removing some of the tumor for viewing under a microscope and other lab testing) is the only way to make sure about. A biopsy is also the best way to tell osteosarcoma from other types of cancer. If the tumor involves bone, it is very important that a surgeon experienced in treating bone tumors does the biopsy. Proper planning of the biopsy location and technique can prevent later complications and reduce the amount of surgery needed later on[19].

Testing the biopsy samples: All samples removed by biopsy are sent to a pathologist to be checked by microscope. Moreover, tests looking for chromosome or gene changes in the tumor cells can be conducted. These tests may assist distinguish osteosarcoma from other cancers that similar to it under the microscope and can sometimes assist to forecast whether the osteosarcoma is likely to respond to therapy[21].

Blood tests: Blood tests is not necessary to diagnose osteosarcoma, however they may be helpful once a diagnosis is made. For instance, high levels of certain parameters in the blood such as alkaline phosphatase and lactate dehydrogenase (LDH) can show that the osteosarcoma may be more advanced than it appears[13].

OSTEOSARCOMA TREATMENT

Huge progresses have been made in the treatment of osteosarcoma during the past 30 years. Researches have found that chemotherapy given before and after surgery will cure one who is suffering from osteosarcoma.

Surgery: Surgery includes the diagnostic biopsy and the surgical treatment. Surgery is an important part of treatment for virtually all osteosarcomas. Anytime possible, it is very essential the biopsy and surgical treatment be planned together. The most important aim of surgery is to eliminate all of the cancer. To make sure that it does not occur, surgeons eliminate the tumor plus some of the normal tissue that surrounds it. It is called a wide excision. Eliminating some normal-looking tissue enhances the chance that all of the cancer is removed. A pathologist will check the tissue under a microscope to make sure if the margins contain cancer cells. If cancer cells were observed at the edges of the tissue, the margins are known as positive margines. Positive margin means that some cancer was left behind. When no cancer cells are observed at the edges of the tissue, the margins are negative. A wide excision with clean margins minimizes the risk that the cancer will grow back where it started[22].

Chemotherapy: Chemotherapy, the use of drugs for treating cancer, is systemic therapy. In this method, the drug enters the blood stream and to reach the cancer cells and destroy them. Chemotherapy is useful for osteosarcoma that has spread through the bloodstream to the lungs and/or other organs or has a high risk of doing so. It is part of the treatment, even though some patients with low-grade osteosarcoma may not receive it[23]. The drugs used to treat osteosarcoma are:

- Methotrexate (given in high doses along with leucovorin to assist prevent side effect
- Doxorubicin (Adriamycin)
- Cisplatin or carboplatin
- Etoposide
- Ifosfamide
- Cyclophosphamide
- Actinomycin D (dactinomycin)
- Bleomycin

Most chemotherapy drugs can cause side effects like nausea and vomiting, loss of appetite, hair loss and mouth sores[23]. The reason is that the chemotherapy can damage the blood-producing cells of the bone marrow, patients may have low blood cell counts.

After osteosarcoma treatment: After treatment for osteosarcoma, the most important concerns for most patients are the immediate and long-term influences of the tumor and its treatment and concerns about probable recurrence of the tumor. Follow-up is essential to check for cancer recurrence or spread, as well as potential side effects of some specific treatments.

CONCLUSION

Bone, a type of dense connective tissue, is hard organ to support and protect the various organs of the body, produce blood cells and store minerals. It has a variety of shapes and a complex internal and external structures. There are, however, various types of bone disorders that require clinical treatments. All in all, the information reviewed in this study provided insight into the bone, the cells, the functios, some disorders and methods of their treatments.

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