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Research Article **Published Date:- 2019-12-05**

The motivational factors and adverse events experienced by healthy volunteers donating bone marrow for research

Background: With the advancement of cell therapy research, there is an increasing need for healthy volunteers (HV) to donate small volumes (30 ml) of human bone marrow (BM). The BM procedure required to procure small volumes is invasive, although short-lived (25 seconds), is not without risk. To ensure a sustainable supply of BM for research and cell therapy, greater information of the risks and factors that motivate HV to donate small volumes of BM will help optimize the procedure and HV enrolment, ensuring donors are fully informed of the potential risks.

Objective: To identify the adverse events (AE) experienced by HV during and after small volume BM procedure and understand the motivating factors that influence HV to donate BM for research.

Method: HV (n = 55) who donated BM (30 ml) for scientific research and provided informed consent were administered a questionnaire to identify the type, duration and severity of AE experienced during and post-BM aspiration; and to determine the motivating factors that influenced their willingness to donate BM.

Results: Pain was experienced by 89% of participants during the BM procedure with moderate grade reported by 40%. One/more of the following AE were experienced by 73% of the volunteers post-BM procedure: pain, fatigue, site reaction, nausea and transient hypotension. AE resolved within an average of three days. The reported motivational factors ranked in the following order: first, to advance research for the benefit of future patients; compensation for participation; free medical check-up; lastly, the research question was interesting.

Conclusion: Young HV, motivated primarily by altruism and financial compensation, risk the occurrence of transient AE following donation of small-volume BM for research.

Research Article **Published Date:- 2019-11-11**

Correlation of plasma protein from MDS, young and elderly patients by SDS-page

Summary: Myelodysplastic Syndrome (MDS) is a heterogeneous group of clonal hematopoietic malignancies characterized by progressive cytopenias, ineffective hematopoiesis, bone marrow hypercellularity and transformation to acute myeloid leukemia (AML).

Objectives: Identify plasma proteins from MDS patients and from two healthy controls groups (young and elderly) by SDS-Page.

Methods: Plasma from 08 healthy young, 08 healthy elderly and 08 MDS patients were used for this study. Proteins were fractionated, precipitated, used for SDS-PAGE gel analysis, stained with comassie brilliant blue, scanned and bands were analyzed.

Results: It was possible to identify in both, 20% fraction and supernatant, proteins that were differentially expressed in each group. The ones that have showed some clinical relevance. Fibronectin was highly expressed only in the young control group. ?2-Macroglobulin was also expressed in both control groups, but it was not expressed in the MDS group. Haptoglobin was highly expressed only in the elderly control and SMD groups.

Conclusion: Protein expression in plasma can be a biomarker for MDS, and may play a key role in the process of aging and hematologic malignancies development.

Review Article **Published Date:- 2019-11-05**

Drug abuse and its ramifications on skeletal system

The purpose of this study is to highlight the drug abuse hazards and preventive aspects. From a public health perspective, substance abuse has long been a source of major concern, both for the individual's health and for wider society as a whole. The UK has the highest rates of recorded illegal drug misuse in the western world. In particular, it has comparatively high rates of heroin and crack cocaine use. Substances that are considered harmful are strictly regulated according to a classification system that takes into account the harms and risks of taking each drug. The adverse effects of drug abuse can be thought of in three parts that together determine the overall harm in taking it. Some addictive substances are more damaging to the skeletal system along with the others. In this review article, an effort has been taken to elaborate the effects of addictive drugs on human highlighting these most problematic substances for bones and also the promising potential prevention aspects of drug abuse.

Letter to Editor **Published Date:- 2019-08-16**

Serum MicroRNA-155 in Acute Graft-Versus-Host-Disease (aGVHD)

Allogeneic hematopoietic stem cell transplant (alloHSCT) is a curative treatment for many hematologic malignancies. Unfortunately, about 30-50% of all recipients undergoing alloHSCT develop acute graft-versus-host-disease (aGVHD), which is associated with high morbidity and mortality [1,2]. Treatment of aGVHD involves the use of immune suppressive drugs such as high dose of steroids that leads to further immunosuppression and risk for opportunistic infections. Often patients are refractory to steroids therapy making the prognosis dismal. Thus, it is critical to identify robust biomarkers to detect aGVHD before onset of clinical symptoms so that therapeutic strategies can be implemented that may result in better treatment responses and less toxicity.

Research Article **Published Date:- 2019-06-21**

Bone marrow histology in CALR mutated thrombocythemia and myelofibrosis: Results from two cross sectional studies in 70 newly diagnosed JAK2/MPL wild type thrombocythemia patients

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The clinical phenotypes in 268 $JAK2^{V617F}$ mutated MPN patients in the Seoul study were PV in 101, ET in 95 and MF in 78 and 56 CALR mutated MPN consisted of PV in none, ET in 40 and MF in 16 cases. CALR mutated MPN patients were younger than $JAK2^{V617F}$ mutated MPN patients (mean ages 57.5 and 66 years), had lower values for values for leukocytes (8.6 vs $11.9x10^9$/L) and higher values for platelets (898 vs $643x10^9$/L respectively). Bone marrow histopathology in 268 $JAK2^{V617F}$ mutated MPN patients in the Seoul study was featured by an increased erythropoiesis and megakaryopoiesis (EM) in 13.5%, an increased erythropoiesis, megakaryopoiesis and granulopoiesis (EMG) in 31.3%, a normocellular megakaryocytic (M) proliferation in 29,1%, a megakaryocytic and granulocytic (MG) proliferation with a relative reduction of erythropoiesis in post-ET and Post-PV myelofibrosis in 26.2%. The bone marrow histology in 56 cases of CALR mutated MPN show a predominantly increased megakaryopoiesis (M) in two thirds and an increased megakaryopoiesis and granulopoiesis (MG) with a decreased erythropoiesis in one third.

Thirteen consecutive CALR MPN patients in the Belgian & Dutch cross sectional study presented with thrombocythemia associated with a typical PMGM bone marrow histology in 11 and myelofibrosis in 2 cases. All 11 thrombocythemia and 2 myelofibrosis CALR mutated MPN patients did not have constitutional symptoms and did not suffer from microvascular erythromelalgic disturbances, major thrombosis at platelet counts between 400 and $1000x10^9$/L. There was an occurrence of hemorrhages at platelet counts above $1000x10^9$/L in two CALR thrombocythemia cases.

Bone marrow histology of CALR mutated thrombocythemia in the Seoul and Belgian/Dutch study showed loose clusters of large megakaryocytes (M) with bulky, cloud-like nuclei with a normal or a minor reduction of erythropoiesis and no increase in reticulin fibers grade 0 or 1 (RF 0 or 1). CALR thrombocythemia patients show various degrees of increased bone marrow cellularity due to dual megakaryocytic and granulocytic (MG) proliferation featured by large megakaryocytes with roundish bulky nuclear forms and cloud-like clumsy nuclei, which are almost never seen in $JAK2^{V617F}$ ET and PV. Assessment of allele burden is an independent and most important factor for all molecular variants MPN disease burden. Overt myelofibrosis with advanced post PV and or ET myelofibrosis at the bone marrow level occurred in one third (30%) of 208 evaluable JAK2 MPN patients and in 8 (14%) of 56 CALR MPN patients in the Seoul study.

Case Report **Published Date:- 2019-05-13**

The forgotten player in the surgical history

The research concerning a preventive treatment of an osteoporitic femoral neck fracture started in 1990 because the surgical procedure of unstable femoral neck fractures is difficult. After effects are frequent and their number will increase in the next decade. The goal is to reinforce the femur with a biomaterial acting as a bone graft.

Natural coral is bioresorbable and biocompatible. It acts as an autofocus bone graft for reconstruction of either cortex or cancellous bone and increases their mechanical resistance.

This work shows evidence of new bone formation in an osteoporotic unbroken femoral neck femur. Consequently, the preventive surgical treatment of osteoporosis should be taken in consideration [1]. The purpose of this work is to show the results on the mineralization of the cancellous bone of an upper femoral metaphyses when a natural biomaterial is set in an unbroken osteoporotic femoral neck.

Summary: Mrs. L is an 84 years old lady. Her osteoporotic unbroken right hip was grafted preventively with a biomaterial in order to prevent the high risk of break in case of fall. The biomaterial used is beads of natural coral. The reasons of this preventive treatment is discussed, as well as the choice of the biomaterial. The results are shown including a two years follow up.

Brief History: Before going further, few words of history. Three centuries BC, an Aristote's follower, Théophraste thinks that Natural coral is a petrified plant.

For Ovide natural coral is a soft alga air-hardening.

Al Biruni classes it among animals, because that respond to touch.

At the beginning of the XVIIth century, Marsigli thinks that they are flowers which open out there in aquarium.

The French Jean-André Peyssonnel, a young naturalist, says as Biruni, that in fact, corals are animals.

At last, Buffon claims: These marine plants, were classified first in the rank of minerals, then in those of plants, and finally in that of animals.

Natural coral is obviously an animal.

After the Second World War, coral samples were analyzed by American scientists. Among 800 corail species, 3 where specially analyzed: Acropora, Porites and Libophylia.

Mrs Nane Guillemin did in France her PHD on natural coral and with her team made a complete fundamental analysis (physical, chemical and biological properties) of the material, while the American scientists worked on the chemical bone's properties.

In France, Pr Ohayoun and his team worked on the surgical application in the dental field, Dr. Yves Cirotteau in the orthopedic surgery, specifically for osteoporotic disease and for the traumatologic field

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Research Article **Published Date:- 2019-04-17**

The PVSG/WHO versus the Rotterdam European clinical, molecular and pathological diagnostic criteria for the classification of myeloproliferative disorders and myeloproliferative neoplasms (MPD/MPN): From Dameshek to Georgii, Vainchenker and Michiels 1950-2018

The present article extends the PVSG-WHO criteria into a simplified set of Rotterdam and European Clinical, Molecular and Pathological (RCP/ECMP) criteria to diagnose and classify the myeloproliferative neoplasms (MPNs). The crude WHO criteria still miss the masked and early stages of ET and PV. Bone marrow histology has a near to 100% sensitivity and specificity to distinguish thrombocythemia in *BCR/AB*L positive CML and ET, and the myelodysplastic syndromes in RARS-T and 5q-minus syndrome from BCR/ABL negative thrombocythemias in myeloproliferative disorders (MPD). The presence of JAK2V617F mutation with increased erythrocytes above 6x10 ^{12}/L and hematocrit (>0.51 males and >0.48 females) is diagnostic for PV obviating the need of red cell mass measurement. About half of WHO defined ET and PMF and 95% of PV patients are JAK2^{V617F} positive. The combination of molecular marker screening JAK2^{V617F}, JAK2 exon 12, MPL^{515} and CALR mutations and bone marrow pathology is 100% sensitive and specific for the diagnosis of latent, early and classical ECMP defined MPNs. The translation of WHO defined ET, PV and PMF into ECMP criteria have include the platelet count above 350 x10^{9}/l, mutation screening and bone marrow histology as inclusion criteria for thrombocythemia in various MPNs. According to ECMP criteria, ET comprises three distinct phenotypes of true ET, ET with features of early (“forme fruste” PV), and ET with a hypercellular erythrocythemic, megakaryocytic granulocytic myeloproliferation (EMGM or masked PV). The ECMP criteria clearly differentiate early erythrocythemic, prodromal and classical PV from congenital polycythemia and idiopathic or secondary erythrocytosis. The burden of JAK2V617F mutation in heterozygous ET and in homozygous PV is of major clinical and prognostic significance. JAK2 wild type MPL^{515} mutated normocellular ET and MF lack PV features in blood and bone marrow. JAK2/MPL wild type hypercellular ET associated with primary megakaryocytic granulocytic myeloproliferation (PMGM) is the third distinct CALR mutated MPN. The translation of WHO into ECMP criteria for the classification of MPNs have a major impact on prognosis assessment and best choice for first line non-leukemogenic approach to postpone potential leukemogenic myelopsuppressive agents as long as possible in ET, PV and PMGM patients.

Research Article **Published Date:- 2019-04-15**

[Primary myelofibrosis is not primary anymore since the discovery of MPL515 and CALR mutations as driver causes of mono-linear megakaryocytic and dual megakaryocytic granulocytic myeloproliferation and secondary myelofibrosis]

Primary myelofibrosis (PMF) is a distinct clinicopathological myeloproliferatve disease (MPD) not preceded by any other MPD ET, PV, CML,... Combined use of bone marrow histology and increased erythrocyte counts above 5.8x10^{12}/L can replace increased red cell mass at time of presentation as the pathognomonic clue for the correct diagnosis of hetero/homozygous or homozygous mutated PV. Erythrocyte counts are in the normal range below 5.8x10^{12}/L in heterozygous JAK2^{V617F} mutated ET and prodromal PV but above 5.8x10^{12}/L in heterozygous-homozygous or homozygous mutated PV. The bone marrow cellularity and morphology in pre-fibrotic ET, prodromal PV and PV carrying the JAK2^{V617F} mutation are overlapping showing clustered increase of large mature pleomorphic megakaryocytes (M) with no increase of cellularity (<60%) in ET. The bone marrow is hypercellular (60%-80%) due to increased erythropoiesis megakaryopoiesis (EM) in prodromal and classical PV and trilinear hypercellular (80%-100% due increased megakaryopoiesis, erythropoiesis and granulopoiesis (EMG) in advanced PV and masked PV. Bone marrow cellularity ranging from normal (<60%) in ET to increased erythropoiesis (EM) in prodromal PV to hypercellular (80-100%) in advanced PV and masked PV largely depends on increasing JAK2^{V617F} mutation load from low to high on top of other biological MPN variables like constitutional symptoms during long-term follow-up. MPL^{515} mutated ET is featured by an increase of clustered small and giant megakaryocytes with hyper-lobulated staghorn-like nuclei in a normal cellular bone marrow. The third entity of pronounced JAK2/MPL wild type ET associated with primary megakaryocytic granulocytic myeloproliferation (PMGM) without PV features proved to be caused by calreticulin (CALR) mutation. CALR mutated thrombocythemia is characterized by dual proliferation of megakaryocytic and granulocytic bone marrow proliferation of dense clustered large to giant immature dysmorphic megakaryocytes with bulky (bulbous) hyperchromatic nuclei, which are not seen in MPL^{515}-mutated Thrombocythemia and JAK2^{V617F}-Thrombocythemia, prodromal PV and classical PV.

Research Article **Published Date:- 2019-03-01**

[European Clinical Laboratory, Molecular and Pathological (ECMP) criteria for prefibrotic JAK2V617F-Thrombocythemia and Polycythemia Vera versus MPL515- and CALR-Thrombocythemia and Myelofibrosis: From Dameshek to Michiels 1950-2018]

The broad spectrum of heterozygous versus homozygous JAK2V617F mutated MPN consists ET, ET with early features of PV (prodromal PV), classical PV, masked PV, advanced PV and post-PV myelofibrosis. Combined use of bone marrow histology and increased erythrocyte counts above 5.8x1012/L can replace increased red cell mass at time of presentation as the pathognomonic clue for the correct diagnosis of hetero/homozygous or homozygous mutated PV. Erythrocyte counts are in the normal range below 5.8x1012/L in heterozygous JAK2V617F mutated ET and prodromal PV but above 5.8x1012/L in heterozygous-homozygous or homozygous mutated PV. The bone marrow cellularity and morphology in pre-fibrotic ET, prodromal PV and PV carrying the JAK2V617F mutation are overlapping showing clustered increase of large mature pleomorphic megakaryocytes (M) with no increase of cellularity (<60%) in ET. The bone marrow is hypercellular (60%-80%) due to increased erythropoiesis megakaryopoiesis (EM) in prodromal and classical PV and trilinear hypercellular (80%-100% due increased megakaryopoiesis, erythropoiesis and granulopoiesis (EMG) in advanced PV and masked PV. Bone marrow cellularity ranging from normal (<60%) in ET to increased erythropoiesis (EM) in prodromal PV to hypercellular (80-100%) in advanced PV and masked PV largely depends on increasing JAK2V617F mutation load from low to high on top of other biological MPN variables like constitutional symptoms during long-term follow-up. MPL515 mutated ET is featured by an increase of clustered small and giant megakaryocytes with hyper-lobulated staghorn-like nuclei in a normal cellular bone marrow. The third entity of pronounced JAK2/MPL wild type ET associated with primary megakaryocytic granulocytic myeloproliferation (PMGM) without PV features proved to be caused by calreticulin (CALR) mutation. CALR mutated thrombocythemia is characterized by dual proliferation of megakaryocytic and granulocytic bone marrow proliferation of dense clustered large to giant immature dysmorphic megakaryocytes with bulky (bulbous) hyperchromatic nuclei, which are not seen in MPL515-mutated Thrombocythemia and JAK2V617F-Thrombocythemia, prodromal PV and classical PV.